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ELECTROPHYSIOLOGICAL STUDIES OF NERVE AND REFLEX ACTIVITY IN NORMAL MAN

I. Identification of Certain Reflexes in the Electromyogram and the Conduction Velocity of Peripheral Nerve Fibres[1]

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Received for publication February 2, 1950

The studies reported in this and the succeeding two communications were undertaken in the course of investigating certain peripheral manifestations of spinal cord reflex activity in man. Some of the electrical patterns evoked by mixed nerve stimulation have been previously described—others to be presented in this paper are new. It became apparent that alteration of such peripheral sensory and motor mechanisms by ischemic block introduced a useful modification in the analysis of these patterns. A review of the literature pertinent to the effects in man of such blocks revealed several divergent observations and interpretations. These were especially confusing in regard to the details and mechanisms of the post-ischemic state. The phenomena have, therefore, been reinvestigated from a descriptive standpoint. Likewise, the concomitant alterations in certain objective electrical patterns evoked by peripheral nerve stimulation have been studied under these conditions. Wherever possible, information gained in this manner will be used in interpretation of mechanisms underlying the clinical findings. This first paper describes some of the patterns normally evoked by stimulation of a mixed peripheral nerve in man. Preliminary deductions will be made regarding their interpretation. The analysis will be extended in subsequent papers wherein the effects of ischemia and the post-ischemic state will be described and discussed.

Although the responses of motor nerves and muscles in man to constant (galvanic) and alternating (faradic) stimulation have been noted

[1] These investigations have been supported financially, for the most part, by the Lewis J. and Harriet S. Lederer Fund of the Johns Hopkins University.

for years, it is only during this century that more refined techniques have been employed. Piper (1912) applied effective electrical stimuli to accessible mixed peripheral nerves and recorded muscle action potentials through the intact skin. Hoffmann (1922) carried out more precise recording of the motor effects of such stimulation and, in addition, made an accurate analysis of a prominent stretch reflex response (Lloyd, 1943a) which was represented in the electromyograms of calf muscles following submaximal stimulation of the posterior tibial nerve.

With the later development of more sensitive electromyographic techniques, the purely motor effects of peripheral nerve stimulation in man have received considerable attention. The papers of Harvey and Masland (1941), Hodes, Larrabee, and German (1948), and Petersen and Kugelberg (1949), describe detailed studies. On the other hand, although noted by most observers interested in evoked electromyography, even the reflex responses of Hoffmann have been subjected to little investigation. Increased knowledge of peripheral nerve fibre activity (Erlanger and Gasser, 1937) and the functional organization of the mammalian spinal cord (Lloyd, 1944), indicate the need for a precise study of reflex patterns in human material. Only Kugelberg (1948) has subjected the outbursts of reflex activity in spasticity to analysis and shown the relative contributions of A and C fibres (Gasser and Erlanger, 1929) to them. The present paper deals entirely with phenomena transmitted through rapidly-conducting fibres of the A group in normal man.

PROCEDURE

Eight different young adult subjects were used. Experiments dealing with sensory experiences were always repeated at least once on the authors of this report. In view of the uncertainty of actual anatomical and physiological changes present in clinical material, and the possible fallacies in sensory interpretation, no patients with neurological disease or damage were studied. The experiments were performed at a room temperature which varied from about 22° C. to about 27° C. from day to day.

The general experimental arrangement is indicated in Figure1.[2] The extremity, usually left upper or lower, was comfortably supported in a convenient position. Monopolar cathodal shocks (S), of about 0.5 msec. duration, were applied through

[2] Dr. S. A. Talbot designed and supervised the construction of most of the equipment used in these studies. Without his experience and inestimable help, they would not have been possible.

the intact skin to the ulnar or posterior tibial nerve behind the elbow or knee, or at different sites above wrist or ankle, dependent on the nature of the experiment.

Muscle action potentials were led through paired surface electrodes, or through unipolar needles insulated to the tips, from the hypothenar group, short flexor muscles of the foot, or from anterolateral or calf muscles. On occasion a concentric needle electrode (Adrian and Bronk, 1929) was used for sharper localization. In the results to be reported, unless stated otherwise, the nature of the electrode was found to be immaterial. For recording from nerves, the method of Dawson and Scott (1949)[3] was employed. Paired brass cups containing Bentonite paste were placed over the ulnar nerve above the elbow, or the posterior tibial nerve in the popliteal fossa. Action potentials from these electrodes were recorded, after ade-

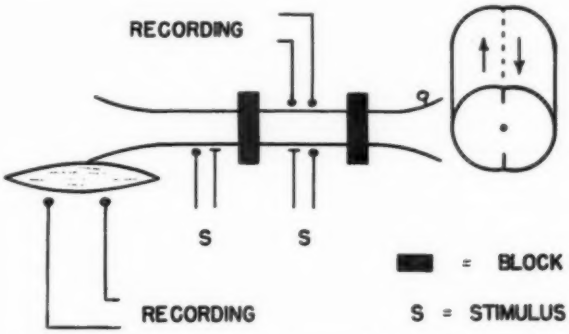

FIG. 1. Diagram of experimental arrangement for a typical experiment. Stimuli (S) applied at different levels over the mixed nerve. Recording from muscle or nerve. In some experiments, the limb was occluded by a pressure cuff, or the nerve blocked, at one or both of the sites indicated.

quate amplification, on the sweep of a cathode-ray oscilloscope. For check on consistency, all determinations were repeated from six to twenty times on separate sweeps at intervals which were never less than 1 second. Continuous registration of muscle activity was effected by the use of bifilar mirror galvanometers of 3000 c.p.s. natural frequency reflecting on moving paper. The sites of recording muscle and nerve activity are indicated in the diagram. Measurement of all records was made after projection at high magnification on graph paper.

Intraneural procaine blocks, when used, were to the ulnar nerve at the level of the elbow. Four or five cc. of two per cent procaine with epinephrine were injected with each block. It was found that considerable skill was required to achieve

[3] Dr. George Dawson kindly sent unpublished details of his method, and examples of his proofs that he is recording (for the most part, at least) from sensory fibres.

the actual intraneural injection which is necessary for complete interruption of conduction and for adequate duration of the block.[4] Faulty placement may give a short-lasting appearance of complete block which, however, becomes progressively less effective and leads to inaccurate observations.

All sites of stimulation and recording were marked and measured in relationship to a fixed point at the conclusion of each experiment.

RESULTS AND INTERPRETATIONS

Certain sensory and motor phenomena follow maximal percutaneous electrical shocks to a mixed peripheral nerve. The subject experiences a momentary definite, though not painful, sensation at the site of stimulation, and often in the distal distribution of the nerve (cf. Kugelberg, 1944). The sensation is a characteristic tingling one which is readily recognized, though it may be difficult to describe. It is quite different from that evoked by stimulating nearby skin areas. The shock to the nerve is followed by a brisk contraction of muscles supplied by the affected nerve. When the ulnar nerve is stimulated at the wrist, contraction is limited to the ulnar-innervated small muscles of the hand. Likewise, when the posterior tibial nerve is stimulated at the ankle, only small muscles of the foot are involved.

The electrical concomitants of these motor and sensory effects have been recorded and are illustrated in the figures of this paper. For purposes of description, they will be considered under five headings, arbitrarily designated *M*, *F*, *H*, and *Late waves*, and *Nerve Action Potentials*.

1. *M Waves and Conduction Velocity of Motor Nerve Fibres.*

Figures 2 and 3 are representative of action potentials recorded from muscles of the hypothenar group. The intensity of the shock to the ulnar nerve at the elbow was gradually increased throughout the sequence of records in the two figures. It is apparent that, once suprathreshold stimulation had been achieved, the stimulus artefact was followed by a polyphasic action potential which progressively increased to a maximal value. This activity in the muscles is evoked by efferent motor fibres. The varying polyphasic form of the deflections from one

[4] The authors take pleasure in expressing their gratitude to Dr. M. Edgerton of the Department of Surgery for his skill and continued cooperation in performing all the blocks.

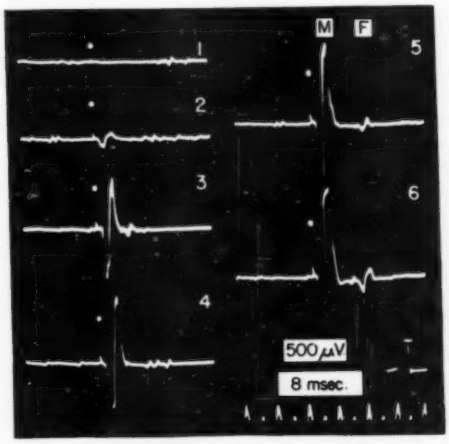

FIG. 2. Action potentials from hypothenar muscles recorded on cathode ray oscilloscope. Surface electrodes. Single cathodal shocks of progressively increasing intensity to ulnar nerve at elbow. Stimulus artefact indicated by dot in the records of this and subsequent figures. Calibration—500 microvolts. Time—8 msec.

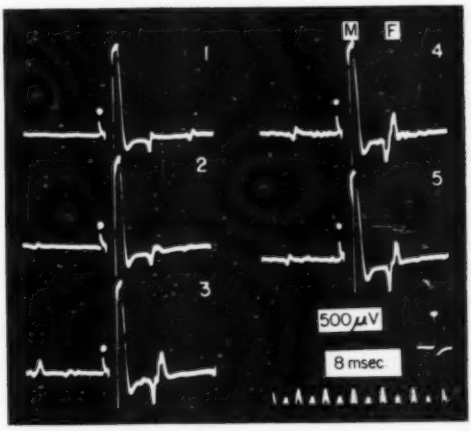

FIG. 3. Continuation of Figure 2 with yet stronger stimuli. Same calibration and time scale.

experiment to another is due to different placement of the recording electrodes and the non-localizing recording of this type of lead. Since

the features of this phase of the normal human muscle action potential have been well described by Hodes, Larrabee, and German (1948), Petersen and Kugelberg (1949), and others, they need no further comment here. For ease of description, however, the deflections have been designated *M waves*.

The latency from the time of nerve stimulation to the onset of the M wave depends, for all practical purposes, on the length of motor nerve between the site of stimulation and the muscle, and on the velocity of the most rapidly conducted impulses. When the same nerve trunk is stimulated successively at two places (Hodes, Larrabee, and German, 1948) differences in latency may be assumed to measure the conduction time of the fastest impulses over the segment of nerve

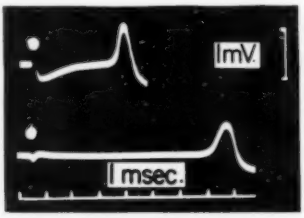

FIG. 4. Action potentials from hypothenar muscles with rapid sweep of cathode ray beam. Only first deflections of M wave shown. Maximal shocks to ulnar nerve: Record 1—stimulation above wrist; record 2—stimulation 20.3 cm. more proximally. Time—1 msec..

between the sites of stimulation. In Figure 4 are records from a typical experiment to exemplify these differences in latency. The prominent deflections represent the first component of the M wave. In the upper record, the ulnar nerve was stimulated at a site which was 20.3 centimetres distal to that of the lower record. In this experiment, the average velocity of motor impulses over the whole forearm segment was 55 metres per second. In all eight subjects of this study, velocities of motor impulses in the ulnar nerve between elbow and wrist, and in the posterior tibial nerve between popliteal fossa and ankle, varied between 45 and 68 metres per second. These values are in keeping with those found by Hodes, Larrabee, and German (1948) for the same stretches of nerve.

When the nerves were stimulated not only at proximal and distal sites, but also at various intermediate points, series of action potentials of different latencies were obtained from the innervated muscle group. These latencies have been used in determining conduction rates for proximal and distal portions of the same nerve trunk. It has been found in each of five different subjects that the velocities of motor impulses in the ulnar nerve trunk, for example, were from 10 to 20 metres per second greater in proximal, than in distal, segments of the forearm region. This was true whether the nerve was excited by shocks which were submaximal or well above maximal for the motor fibres. In the experiment represented by Figure 4, in which the average velocity of motor impulses over the whole forearm was 55 metres per second, conduction rates of the most rapidly conducting fibres of the lower 8 centimetres, and the upper 13 centimetres, were respectively 43 and 63 metres per second. There is evidence, therefore, that velocities of impulses traversing the motor fibres of nerve trunks are decreased as they proceed distally. Helmholtz and Baxt (1870) found similar distal slowing in motor fibres in man when the latencies of mechanical contractions evoked by nerve stimulation at several sites were likewise compared. This important observation, however, seems to have been neglected by later workers. The present confirmatory findings indicate that this slowing must be taken into consideration whenever a comparison of velocities in different segments of a motor nerve in man is undertaken.

2. F Waves and Conduction Velocity of Certain Afferent Nerve Fibres.

In Figures 2 and 3, the initial M wave recorded from hypothenar muscles was followed, some milliseconds later, by a smaller, quite separate, potential change. In this particular experiment, it appeared about 30 milliseconds after the stimulus artefact and 16 milliseconds after the completion of the M component. It tended to increase in amplitude with increasing strength of nerve stimulation up to intensities supramaximal for the M wave. This component, which has been designated the *F wave*, varied in prominence in different subjects. In some, as in the experiment illustrated by Figures 2 and 3, it was large and evident at low sensitivity of the amplifier. In others, it was apparent only with relatively high amplification. In all subjects it was

variable in its appearance. Some shocks were followed by virtually no F waves; others by very large ones. Such variability does not seem dependent on any particular relationship to preceding volleys—it was strikingly seen, for example, with regular stimulation at a rate of one per second. In most instances, as in the experiment from which Figures 2 and 3 were derived, F waves appeared with a certain level of stimulation intensity and then tended to increase in amplitude with stronger nerve volleys. In other cases, the deflections reached their maximal amplitude with only moderately intense stimulation of the nerve, and increased no further with stronger volleys. In no case, however, have

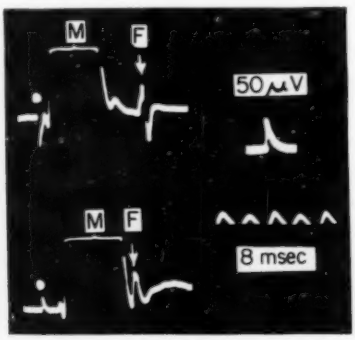

FIG. 5. Action potentials from hypothenar muscles at high amplification. Surface electrodes. Single maximal shocks to ulnar nerve. In upper record, the site of stimulation was 22 cm. distal to that of lower record. Calibration—50 microvolts.

they declined as stimulation intensity was increased, in contrast to the H waves which will be discussed in a later section of this paper. In any one subject F waves were remarkably constant in their time relationships. In one or two experiments, however, there have been sporadic increases in latency of one or two milliseconds without any evident change in the form of the response. In other instances, there has been an inversion of the deflection without any change in latency.

When the stimulating electrode was moved to a more distal position in the forearm, the F wave appeared after a considerably increased latent period, although the latency of the M wave was diminished. The records of Figure 5 were taken from such an experiment. High

amplification used in order to accentuate the F waves made it impossible to record the entire configuration of the M wave. Nevertheless, the beginning of its initial upward deflection is readily seen. The latency from the stimulus artefact to the F wave was only 26 milliseconds with stimulation at the elbow, but 31 milliseconds when the shock was moved to the low forearm. Whereas Figures 2, 3, and 5 were taken from experiments in which responses of hypothenar muscles to ulnar nerve stimulation were being investigated, similar F waves have been recorded from small muscles of the foot when the posterior tibial nerve was stimulated, and from anterolateral muscles following peroneal nerve volleys. In neither limb did F waves appear following stimulation of nerve trunks other than those which actually innervated the muscles which have so far been examined. Clearly then, the initial M deflection, recorded most readily from certain small muscles in the hand and foot, is followed by a second deflection, herein designated F. In the case of the latter, the latency is greater when the point of nerve stimulation is closer to the muscle groups, whereas that of the M wave is less.

F waves have been noted in the records of other observers—Dawson and Scott (1949), Kugelberg (1946), Hoffmann (1922), and others. They have usually been disregarded or considered reflex in origin and likened to very prominent stretch reflexes which can be recorded from calf muscles (Hoffmann, 1922). These interpretations must be examined.

F waves were absent when the ulnar nerve was stimulated distal to a complete procaine block of the nerve at the elbow. This shows that they cannot be due to repetitive firing of motor nerve, myoneural junction, or muscle. Their time courses rule out any possibility that they could be secondary to stimulation of peripheral nerve terminations by the action potential of active muscle (Lloyd, 1942). They appear, therefore, to result from impulses discharged from the central nervous system. It is important to decide whether this discharge is caused by impulses which travel antidromically up the axones of motor neurones (Renshaw, 1941), (Lloyd, 1943b) or whether it represents a true reflex response.

With either interpretation, the difference in F wave latency obtained by stimulation of the ulnar nerve trunk proximally and distally must be considered due to the time taken by impulses to travel in a central direction along some fibres between the points of stimulation. If these

were motor fibres, and we assume that impulses in motor axones are conducted antidromically at the same velocity as those traveling dromically, the difference in latency between F waves evoked from the two nerve sites should be the same as that between M waves which follow stimuli at those same points. This has not been found to be the case. In repeated experiments on each of five subjects, velocities of the centripetal impulses which initiate the F wave response, based on differences in latency, have been found to be less than those in the same stretches of motor fibres by an average of 10 metres per second. In the experiment illustrated by Figure 5, for example, the values were 48 metres per second for impulses in the afferent pathway, and 59 for those in the motor fibres.

The differences in latency, and hence in total conduction time, between the fibres of the afferent limb of the F response and motor fibres are increased by ischemia. It will be shown in a subsequent paper (Magladery, McDougal, and Stoll, 1950) that F waves elicited by nerve stimulation distal to a pressure cuff are progressively delayed by a matter of several milliseconds at a time early in ischemia when there is no increase in latency of the M waves evoked by nerve stimulation proximal to the occluding cuff.

These results are not readily compatible with an interpretation of F waves based on antidromic firing. They indicate, on the contrary, that the waves are produced through the medium of a reflex arc, of which the afferent fibres are more slowly conducting than motor fibres in the same segment of nerve trunk.

3. *H Waves and Afferent Fibre Conduction Velocity*

The potential changes accompanying stretch reflexes which Hoffmann (1922) described and clearly identified with tendon reflexes, are obtained from calf muscles following submaximal stimulation of the posterior tibial nerve in the popliteal region. The deflections are readily found following the M waves in the muscle action potential. They are not evoked in these muscles when other nerves of the region are stimulated. For purposes of description, they are here designated as *H waves*. Figures 6, 7, and 8 illustrate action potentials recorded through surface electrodes from calf muscles. The intensity of the stimulus to the posterior tibial nerve in the popliteal fossa was progressively increased

throughout the sequence of records in Figure 6. The effect of diminishing intensity from virtually maximal is shown in Figure 7, taken from the same experiment. It is apparent from Figure 6 that with just suprathreshold stimulation only a minimal M response occurred. With progressively stronger shocks, the M wave increased but was followed by a much more rapidly growing deflection appearing about 19 milliseconds later, the H wave. The latter reached a maximal amplitude with only moderate stimulation intensity. With yet stronger shocks, however, as shown by succeeding records of the figure, the M deflec-

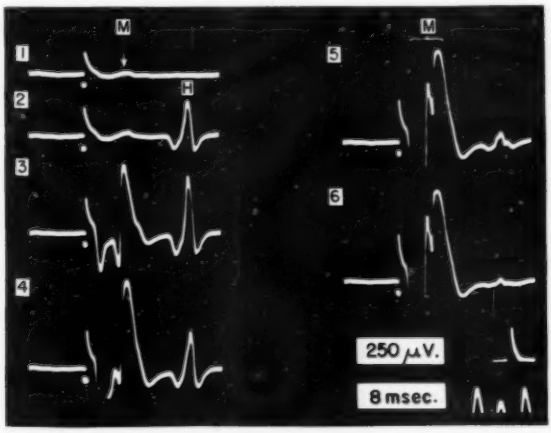

FIG. 6. Action potentials from calf muscles. Surface electrodes. Single shocks of increasing intensity to posterior tibial nerve in popliteal fossa. Calibration—250 microvolts. See text.

tion increased to a maximal value (record 6), whereas the H wave decreased. The converse is seen in records of Figure 7. The small H deflection of record 1 was evoked by almost maximal stimulation strength. With shocks of decreasing intensity (succeeding records), this deflection increased progressively while the M wave diminished. Eventually, however, the H wave faded away just before final extinction of M.

This relationship of the amplitude of the H wave to stimulus intensity is a constant feature of this experimental arrangement, pro-

vided that there is accurate placement of the stimulating electrode over the nerve, and shocks of adequate strength are available. When these

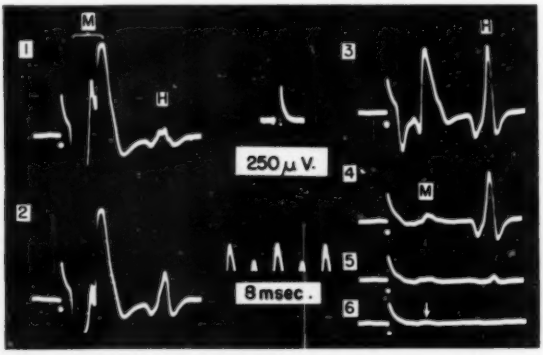

FIG. 7. Continuation of Figure 6. Action potentials from calf muscles following shocks decreasing from almost maximal intensity to posterior tibial nerve in popliteal fossa. Calibration—250 microvolts. See text.

FIG. 8. Action potentials from calf muscles. Surface electrodes. Single shocks of similar submaximal intensity to two points over posterior tibial nerve in popliteal fossa. In upper record, the site of stimulation was 9.0 cm. distal to that of lower record. Arrows indicate beginnings of deflections.

criteria are not fulfilled, maximal stimulation does not occur and results such as are seen in the last two or three steps of Figure 6 may not appear, simply because the stimulus is not strong enough. When stim-

ulation is then made adequate, the above-mentioned striking relationship is revealed.

Hoffmann (1922) used the observation of the diminution of H waves with strong nerve stimulation in his analysis of their significance. He pointed out that stimulated fibres conduct impulses centrally as well as distally. With intense mixed nerve stimulation, most motor fibres are activated in this fashion. Under these circumstances, a reduction in size of the reflex response as the strength of stimulus is increased, must indicate that the excitatory potentiality of the reflex arc has ended before such antidromic impulses reach anterior horn cells, or motoneurones recover from a refractory state. The afferent pathway for such an arc must, therefore, consist of rapidly conducting fibres and central delay must be very short. His deductions on both these points were remarkably accurate in the light of subsequent detailed animal studies (Lloyd, 1943a). The results of the present experiments have elaborated the findings and interpretations of Hoffmann.

When, as in the experiment illustrated by the records of Figure 8, the posterior tibial nerve was stimulated at two separate sites in the popliteal fossa, the relationships of the M and H waves changed. Record 1 shows the alteration produced when the point of stimulation was nine centimetres distal to that evoking the deflections of record 2. Whereas the M wave in the former began 3.5 milliseconds after the stimulus artifact, a comparable figure of 5.5 milliseconds was found in record 2, where stimulation was more proximal. On the contrary, the latency of the H wave was 27 milliseconds in record 2, and 28.5 milliseconds in the first record. An increase in latency as the stimulating electrode is moved distally along the nerve, already described for F waves, is thus also found in the case of H waves. The changes in latency of the M waves indicate a maximal motor conduction rate of 45 metres per second, whereas those of the H waves indicate a highest afferent velocity of 60 metres per second. In view of the depths of tissue intervening in this region between stimulating electrode and nerve, these figures cannot be accepted as absolute. Indeed, in all four subjects examined in this manner, considerable differences were found, with motor conduction rates ranging from 66 to 45. In each, however, the afferent fibres were consistently found to conduct about half again as rapidly as the motor fibres.

It is pertinent at this juncture to compare some of the features manifested by the previously described F waves obtained from small hand and foot muscles with those of H waves. Both, as indicated above, showed varying time relationships to the M waves with different sites of nerve stimulation. Neither reflex was evoked in the appropriate muscle group when a nerve trunk other than that supplying the group was stimulated. The two reflexes responded differently, however, to stimuli of increasing intensity. Whereas H waves were blocked with strong nerve shocks, the F deflections were never found to decrease as intensity of stimulation was increased. An adequate explanation of this difference is found in the relative conduction rates of the nerve fibres concerned. In the H reflex, the afferent fibres were observed (Figure 8) to conduct more rapidly than motor fibres. Of necessity, therefore, afferent impulses reached the spinal cord before antidromic impulses in motor fibres. As animal experiments indicate that the arc of this reflex is monosynaptic (Lloyd, 1943a), the afferent impulses must also have been the first to reach the somata of the motoneurones. If the motor fibres were conducting antidromic impulses, the latter must accordingly have blocked the reflexly-induced impulses in the axones. When the nerve shock was strong enough to excite all motor fibres, blockage of the reflex discharge was complete and the H wave did not appear. In the case of F reflexes, however, the sequence in which impulses reached the spinal cord was reversed; due to the relationship in conduction velocity already described, the antidromic impulses must have arrived ahead of impulses in afferent fibres. The difference in velocity may, in itself, be sufficient to allow the motoneurones to recover from refractoriness before the arrival of the afferent impulses, and thus permit appearance of the F wave even with maximal nerve shocks. Lack of information on conduction rates nearer the spinal cord precludes a decision on this point. It is possible that the afferent impulses are even further delayed in multineurone relays within the cord itself (Lloyd, 1943a).

4. *Late Waves*

When muscle action potentials following mixed nerve stimulation were recorded continuously on moving photographic paper, a more panoramic, though less detailed, picture was seen. Figure 9 is an

example of such a record taken from hypothenar muscles. Compressed M and F waves were clearly present with each stimulation, and in the same relationship seen in previous figures. A dot has been placed over the F wave in some of the records for clarity. These initial components were followed, after a "silent period" (Denny-Brown, 1929), by an outburst of repetitive irregular action potentials of lower amplitude. These outbursts were sometimes of short duration; in other experi-

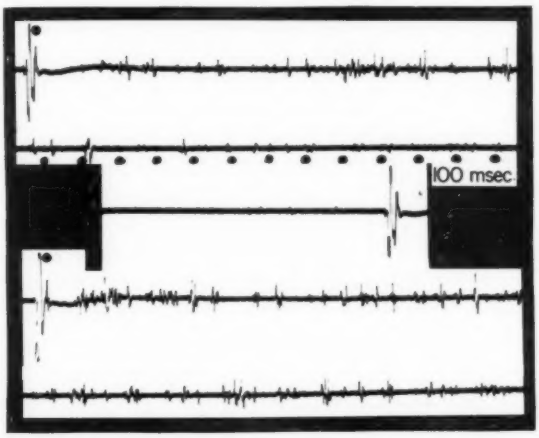

FIG. 9. Action potentials from hypothenar muscles following single maximal, or supramaximal, shocks to ulnar nerve at elbow. Surface electrodes. Continuous recording on moving paper from 3000 c.p.s. galvanometer. Upper 3 tracings in continuity, with stimulus interval of 3.3 seconds. Lower two tracings in continuity at higher gain. Time—100 msec. Amplitude of M wave about 6 mV in tracings 1 and 3.

ments, as in the example shown, they continued for hundreds of milliseconds, or even seconds. In some subjects, exemplified by Figure 9, the *late waves* tended to appear in a series of outbursts of diminishing amplitude and duration. In other experiments on different subjects, the activity was of a more regular pattern. In yet others, no late waves were found. Whatever the pattern, or its occasional absence, it was remarkably uniform in the same subject on repeated examination.

No late waves appeared in the muscle action potentials when the nerve was stimulated distal to a complete procaine block. This indi-

cates that they resulted from activity in the spinal cord. Furthermore, their pattern bears a resemblance to that of weak voluntary movement (Kugelberg, 1946) and to the repetitive non-differentiated A fibre contribution to the plantar response in upper motor neurone disease (Kulgelberg, 1948). A similar pattern has been described by Adrian and Bronk (1929), Denny-Brown (1929), and others, and considered related to reflex firing. More recently, Bernhard and Therman (1947) have specifically attributed a comparable activity in cats to the participation of myotatic reflexes. Whether, however, the present late waves are reflex in origin, as is suggested by the uniformity in these experiments, or represent merely an unrecognized, purely voluntary, shudder in response to a peripheral stimulus, cannot be decided on the present evidence.

5. *Nerve Action Potentials and Conduction Velocity*

The previously described phenomena have been derived from muscles responding to nerve stimulation. It is possible to record action potentials of the nerve impulses themselves through electrodes on the surface of the skin proximal to the site of stimulation (Dawson and Scott, 1949). These may be led in some cases, from the posterior tibial nerve in the popliteal fossa following distal stimulation. Recording in this situation was therefore used whenever these deflections were compared with other phenomena, such as H waves, found prominently in the leg. Recording, however, was difficult and often impossible from that site. In practice, therefore, it was usually found more convenient to stimulate the ulnar nerve in the forearm and record from electrodes placed over this nerve above the elbow. Figure 10 is illustrative of one such experiment. In the lower trace wherein the nerve was stimulated 22.5 centimetres distal to the point of stimulation of the upper record, the latency was greater. Assuming all else constant except length of nerve involved, a conduction rate of 71 metres per second was obtained for the most rapidly conducting nerve fibres contributing to the action potentials. This value is fairly representative of similar determinations on four different normal subjects over the same stretch of nerve, where the range was from 62 to 73 metres per second.

When the stimulus was applied, in particularly suitable subjects, at several different sites in the forearm, comparative determinations of

conduction velocity over different stretches of the same segment of nerve were obtained. In Figure 11 the results of five such experiments in one subject are plotted. The spans between points of stimulation,

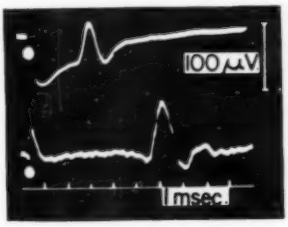

FIG. 10. Nerve action potentials following maximal single shocks to ulnar nerve in forearm. Surface recording over ulnar nerve above elbow. Conduction distances: Upper record—15 cm.; lower record—37.5 cm.. Amplification of lower record is twice that of upper. Time—1 msec..

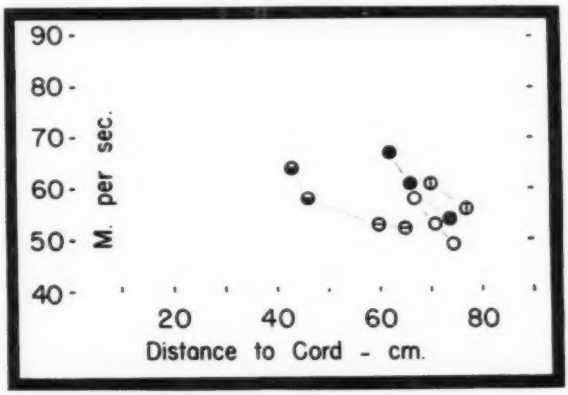

FIG. 11. Sensory nerve conduction rates in ulnar nerve. Ordinates—velocity in metres per second. Abscissa—measured distance from mid-point of nerve stretch examined to C 7 spine. The points indicate results in four separate experiments on different days. In the lowest series, the proximal and distal pair of determinations were made separately.

and distances to an appropriate region over spinal cord, were measured as accurately as possible. Each conduction rate is shown in relation to the distance of the midpoint between two sites of stimulation to the

cord. Although the variations from day to day cannot as yet be explained, the figure demonstrates the progressive increase in velocity found as stimuli were applied more and more proximally. Conduction rates in the lower forearm were, on the average, about 10 metres per second less than those in the upper part of the forearm.

The fact that the recorded conduction rates were greater than those observed in the most rapidly conducting motor fibres in the same segment of nerve, implies that the nerve deflections indicate activity in afferent pathways. Dawson and Scott (1949), who first described these action potentials in man, showed that they appeared following nerve stimulation intensity too low to excite motor fibres. The same authors demonstrated that they appeared only with stimulus strengths which also evoked electrical changes over the contralateral scalp (Dawson, 1947). Further evidence that the deflections indicate activity in relatively low-threshold afferent fibres is provided by experiments with incomplete procaine nerve blocks. Such blocks are unpredictable as to the actual degree of sensory impairment produced. The effects may increase over a period of time or fade. Invariably however, sensory effects appear more readily, and outlast those produced on motor power. The records of Figure 12 were taken from an experiment in which maximal single shocks were applied to the ulnar nerve in the low forearm. Nerve action potentials were recorded above the elbow. The comments beside each tracing describe changes in sensation noted by the subject in response to testing by the usual clinical methods, and alterations observed in his voluntary power. Record 1 shows the control observation. Between records 1 and 2, the ulnar nerve was injected with procaine behind the medial epicondyle and distal to the recording electrodes. Record 2, taken a few minutes later, shows that the action potential was delayed considerably and greatly decreased in amplitude. At this stage, anaesthesia seemed almost complete and no voluntary motor power was evident. Shocks applied through the recording electrodes above the block elicited only minimal movement of the fingers.

Ten minutes later, anaesthesia appeared to be complete and record 3 shows that the nerve potential had decayed even further. Motor power, however, was beginning to return. This was especially evident in the abductor of the little finger. After a further forty minutes, no

sensation could be appreciated throughout the ulnar distribution. Record 4 shows that stimulation in the forearm evoked no action potential above the block. Nevertheless, motor power had recovered

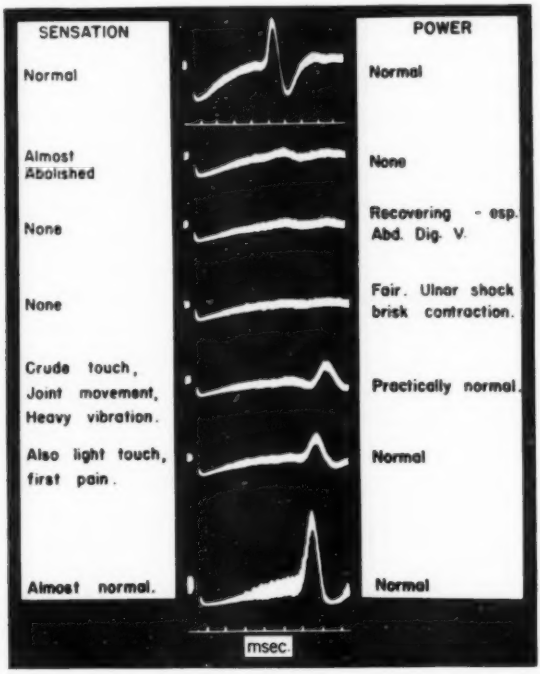

FIG. 12. Nerve action potentials following maximal single shocks to ulnar nerve in forearm. Surface recording over ulnar nerve above elbow. Conduction distance—29 cm.. The stimulus artefact has caused a displacement of the baseline on which the action potential is recorded. In each record 25 sweeps of cathode ray beam were superimposed. Descriptive findings opposite each record.

Incomplete procaine block to ulnar nerve at elbow after record 1. Succeeding records taken 5, 15, 55, 70, 87, 105 minutes after injection. Tracings 1–6 at same amplification—last tracing at higher gain. Time—1 msec

considerably, and stimulation through the recording electrodes above the block was followed by a brisk movement of the ulnar-innervated hand muscles. Record 5 was taken after yet another fifteen minutes.

At this stage crude touch, joint movement, and vibration were perceived by the subject, although heavy pin prick was not felt. Motor power was almost normal. The remaining records of the figure are self-explanatory and trace the gradual recovery of the nerve action potential.

There is considerable evidence, therefore, that nerve action potentials recorded in this fashion are associated with activity in some afferent fibres. It is conceivable that, under normal circumstances of strong nerve stimulation, deflections attributable to centripetal impulses in motor fibres might be buried in the large afferent fibre action potentials, or be reduced in amplitude by a greater temporal dispersion than occurs with impulses in the afferent fibres. Their absence in experiments such as that just described suggests that the latter is more likely to be the correct explanation. In any case it seems evident that part, at least, of the deflections herein recorded represents activity in afferent fibres of higher conduction velocity than motor fibres in the same stretch of nerve trunk. Furthermore, as has been described for other afferent and motor fibres in preceding sections of this paper, conduction is slower distally than proximally in the nerve trunk.

DISCUSSION

It is the purpose of this paper to describe several features of the electrical pattern produced by stimulation of mixed peripheral nerves in man. For clarity, certain deflections occurring in the action potentials led from innervated muscles, and from the skin overlying the nerves themselves, have been designated as M, H, F, and Late waves, and as Nerve Action Potentials.

Nothing has been added to the analysis of the form of the *M waves*, the action potentials initiated in muscle following excitation of motor nerve fibres. However, information of considerable importance about the velocity of impulses in those fibres in man has been obtained. Hodes, Larrabee, and German (1948) remarked on the great contrast between the relatively slow conduction rates detected in certain motor fibres in human limbs and the much higher velocities found in animals and in other motor nerves in man (Piper, 1912). Calculations moreover, based on the assumption that motor impulses were conducted all the way from stimulating electrode to muscle at the velocity determined

by stimulating two widely separated nerve sites, gave conduction times less than the latencies of the muscle action potentials which they actually observed. This discrepancy led those authors to a consideration of a "residual latency", presumably due either to slowed velocity in fine terminal portions of the nerve fibres, or to a delay at the neuromuscular junction. This "residual latency" was, however, much greater than myoneural delays found in other mammalian studies. In the present investigations, the ulnar nerve trunk was stimulated not only at wrist and elbow, but also at various intermediate sites. Contrary to previous assumptions, it was found that impulses in motor fibres showed a progressive slowing as they proceeded distally throughout the extent of this segment of the nerve trunk. Such slowing over long stretches of motor axones might readily explain part of the "residual latencies" of Hodes, Larrabee, and German (1948) and result in calculations of myoneural delays more in keeping with those found in experimental animals.

Further support has been given to the statement of Dawson and Scott (1949) that the nerve action potential, first described by them in man, is due to the passage of impulses in afferent fibres. The results of incomplete procaine blocks indicate that the pathways are not those associated with crude pain perception. On the contrary, they are fibres of relatively low threshold and conduct, over the ulnar nerve trunk between elbow and wrist, and posterior tibial nerve in the popliteal region, at rates greater than those of motor fibres in the same segments—averaging about 70 metres per second. When, moreover, the ulnar nerve was stimulated at various sites between wrist and elbow, it was found that conduction rates in the lower forearm were, on the average, about 10 metres per second less than those obtaining in the upper part of the forearm. This progressive decrease in conduction velocity over distal segments of a mixed nerve trunk is, then, a feature shared by both motor and afferent fibres. The possibility of this occurring has not been considered by most workers in animal physiology, presumably because of the relatively short stretches of nerve under study. In man, however, the longer nerve trunks under investigation enable such comparisons to be made. Indeed, in human studies, this distal slowing, which may well be a phenomenon of nerve fibres generally, must always be taken into consideration.

The reason for the slowing is not clear. Helmholtz and Baxt (1870) postulated that the distally decreased velocity which they encountered in motor fibres was due to a temperature gradient in the limb. The room temperatures, however, at which the present experiments were performed, though not controlled, were always fairly high. In such situations, Pennes (1948) has shown that no significant differences in skin temperature exist throughout the forearm. Under the same conditions, Bazett et al. (1948) found differences in proximal and distal intravascular temperatures which were less than 1 degree centigrade. It seems unlikely, therefore, that a temperature gradient is the major factor in the distal slowing. This view is strengthened by the observation that conduction velocities in motor fibres distal to an occluding cuff (Magladery, McDougal, and Stoll, 1950) do not decrease until long after the cooling which occurs under these conditions (Pennes, 1948).

The slowing more likely indicates a decrease in fibre size (Gasser and Grundfest, 1939) due either to tapering or branching. The results of anatomical studies on this point are conflicting. Dunn (1902) described evident tapering in peripheral nerve fibres. Dale (1900) found a similar gradient in diameter in anterior roots. This could not, however, be verified statistically by Rexed (1944). Instances of branching have been encountered in anatomical (Dunn, 1902) and physiological (Erlanger and Gasser, 1937) studies. The determinations of latencies and conduction rates in the present studies were made on the basis of the beginning of the first deflection of the appropriate nerve or muscle action potential. They deal only with properties of the most rapidly conducting fibres contributing to those action potentials. The demonstration, therefore, of a progressively distal slowing indicates that branching, if it is the explanation, must occur throughout the whole nerve trunk in the forearm and involve all the more rapidly conducting fibres, either in a regular succession, or at multiple sites in the same nerve fibre.

H waves, originally described by Hoffmann (1922), were shown by him to be associated with stretch reflexes. His demonstration that they were abolished by maximal mixed nerve stimulation has been repeated. His deduction that they were subserved by afferent fibres of high velocity has been confirmed by the demonstration that conduction

rates of these afferent fibres are greater, in the popliteal region, than those of motor fibres in the same segment. It is of interest to note that the velocity in the experiment illustrated by Figure 8 was of the order of those which we obtained for the sensory nerve action potentials of Dawson and Scott (1949). This similarity is enhanced by observations that the latter are unrelated to crude pain perception, and that both the H waves and nerve deflections are very susceptible to the depressant effects of ischemia (Magladery, McDougal, and Stoll, 1950).

F waves, recorded from different muscles, bear a certain resemblance to the H deflections. They both show a varying temporal relationship to the M component when the nerve trunk supplying them is stimulated at different sites. Furthermore, it has been shown that conduction rates of the afferent fibres subserving both are different from those of motor fibres in the same segment of nerve. It has been indicated that F deflections, like H waves, are reflex in origin. The former, however, are not diminished by increasing strength of nerve stimulation. On the contrary, they are usually enhanced. This fact in itself suggests that the afferent fibres involved are more slowly conducting than those subserving H waves, thus allowing time for motoneurones to recover from the preceding antidromic firing. This has been directly demonstrated in these studies where conduction rates have been found to be less, and not greater, than those of motor fibres in the same segment of nerve trunk. The known effects of ischemia (Gasser, 1935) are in keeping with these findings. F waves persist after considerably longer periods of circulatory arrest than do H waves (Magladery, McDougal, and Stoll, 1950).

Lloyd (1943a) has analyzed in detail the contributions of various groups of afferent A fibres to spinal reflexes in the cat. There seems little doubt that the two-neurone stretch reflex, subserved by Group I muscle afferent fibres of high conduction velocity, is the counterpart of the stretch reflex of Hoffmann (1922) in man. Lloyd (1943a), however, demonstrated that impulses in Group I fibres of the cat have velocities of about 120 metres per second, whereas much slower conduction rates have been, in this paper, determined for the afferent limb of the H reflex measured in the popliteal region of man. A reasonable explanation of this discrepancy, if human nerves are comparable to those of cats, lies in the evidence of progressive distal slowing of con-

duction rate which has already been discussed. For anatomical reasons, it has so far been found impossible to determine whether, in fact, velocities comparable to those in the cat do obtain nearer the spinal cord in man. Such, however, seems quite possible. If distal slowing does account for the fact that impulses in the afferent fibres contributing to these H reflexes have velocities in accessible regions far below those determined in animals, it seems probable that those subserving F reflexes may likewise have much higher conduction rates nearer the cord than where they have been actually measured in the limb.

The significance of F reflexes needs much further study. It is conceivable that they may be myotatic reflexes with more slowly conducting afferent limbs than those described by Hoffmann (1922), and so thoroughly studied in animals by Lloyd (1943a). The failure, up to the present, to record them when a nerve trunk other than that supplying the muscle group is stimulated, may suggest such an interpretation. There are individuals, normal or otherwise, in whom the usual tendon reflexes cannot be elicited by clinical means, who nevertheless have a relatively, or perfectly, normal posture and gait. They perform fine movements well. This seeming contradiction with the assumed importance of the well known two-neurone stretch reflex in the maintenance of normal muscle tone has always been difficult to understand. The fact (unpublished observations) that we have encountered F reflexes, and failed to find late waves, in small and anterolateral muscles in tabetics and in patients with peripheral neuritis who, despite clinical absence of the usual tendon reflexes and no H waves in calf muscles, were still ambulant and fairly dexterous, might allow conjecture that F reflexes represent an important factor contributing to posture and movement in man. This, however, cannot be substantiated at the present time, and must be considered as speculation. A totally different mechanism may eventually be shown to be represented by them.

SUMMARY

Some patterns of electrical activity evoked by stimulation of mixed peripheral nerves in the limbs of man have been described. Experimental results have been presented which indicate that impulses in both motor and afferent peripheral nerve fibres show a distal slowing.

A component in the electromyogram recorded from certain skeletal

muscles has been identified and shown to be of reflex origin. The afferent pathway of this reflex is composed of fibres which conduct more slowly than those of the well known stretch reflex (Hoffmann, 1922) found in calf muscles.

Certain implications of these observations in the study of peripheral nerve and reflex mechanisms in man have been discussed.

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ELECTROPHYSIOLOGICAL STUDIES OF NERVE AND REFLEX ACTIVITY IN NORMAL MAN

II. The Effects of Peripheral Ischemia[1]

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It has long been known that sensory alterations, paraesthesiae, and certain motor changes accompany and follow ischemia and direct nerve pressure in otherwise normal man. These were clinically described by Goldscheider (1886) and other early authors. It is only in the past twenty years, however, that increased knowledge of nerve fibre activity (Gasser and Erlanger, 1929) and improved investigative methods have prompted more detailed studies. In 1931, Lewis, Pickering, and Rothschild investigated the symptoms and signs accompanying ischemia and its release. In essence, the progress of sensory impairment was reported to be a centripetal one. It was verified that ability to appreciate pain, heat, and cold was retained long after other sensory modalities were no longer felt. Various experimental modifications led the authors to believe that the observed phenomena were due to ischemic changes in the segments of nerve actually compressed by the occluding cuff. These changes were thought to appear first and be most profound in the longest and largest fibres. These subjective observations on ischemia were, for the most part, confirmed by Zotterman (1933), Kugelberg (1944; 1946a; 1946b), and others. In the provocative paper of Weddell and Sinclair (1947), many of the earlier experiments were repeated. Subjective sensations during ischemia were closely analyzed. Contrary to previous reports, it was found that during circulatory arrest paraesthesiae and sensory loss did not follow a strictly centripetal pattern. Changes first appeared in the distribution of an individual nerve—usually the ulnar. The authors concluded, however, with Lewis, Pickering, and Rothschild (1931), that these

[1] These investigations have been supported financially, for the most part, by the Lewis J. and Harriet S. Lederer Fund of the Johns Hopkins University.

phenomena were attributable to direct compression and asphyxia of the segments of the individual nerves under the pressure cuff, and that anatomical differences acounted for discrepancies in their respective findings.

The observations previously described have been mainly concerned with subjective analyses of changes in sensation. Furthermore, they seem somewhat at variance in description and interpretation. Any objective evidence, though not necessarily conclusive, may help to clarify the situation. The following experiments were designed, therefore, with this purpose in mind. Ischemia was studied by the effects it produced on certain phenomena evoked by electrical stimulation of peripheral nerves in man.

PROCEDURE

The arrangement for stimulating peripheral nerves and recording activity has been described in detail in the preceding paper (Magladery and McDougal, 1950).

Ischemia was effected by the use of ordinary sphygmomanometer cuffs. Unless otherwise stated, the cuff—12 centimetres in width—was applied with its distal border about 8 centimetres above the crease in the antecubital fossa, or around the lower thigh. Pressure was maintained at 200 mm. Hg. for about thirty minutes or until voluntary power in the distal muscles was lost. It was then rapidly released. Sensory experiences of the subject, and their temporal relationships, were recorded. Frequent notes on muscle consistency and movements were made.

RESULTS AND INTERPRETATIONS

The paraesthesiae, and the sensory and motor changes, developing during a period of circulatory arrest to a limb have been described by Lewis, Pickering, and Rothschild (1931) and Weddell and Sinclair (1947). The studies on which this report is based add nothing to their basic descriptions, although the cuff pressure used was higher (200 mm. Hg.) and duration of ischemia longer. It might be emphasized, however, that in these experiments, like those of Weddell and Sinclair, a perfectly uniform centripetal spread was not encountered. Most commonly, changes were first noted in the median nerve distribution, rarely in the ulnar. With continued ischemia, however, the whole limb distal to the cuff became involved in a progressive proximally-moving fashion from the fingers to the level of the occluding cuff. Marked sensory impairment always appeared long before any perceptible deterioration in motor power. The latter then diminished

progressively. As with sensation, there was a certain irregularity to this diminution—for example, the long extensor of the thumb usually became powerless before some of the small hand muscles. On the whole, however, the spread of involvement was from the periphery centrally. It is not the purpose of this paper to elaborate on these changes. Differences noted by the various authors are not great and it seems unlikely that discrepancies of interpretation can be resolved by precise clinical descriptions.

During the period of ischemia, progressive alterations occurred in various electrical indices described in a previous paper (Magladery and McDougal, 1950). The headings to be used will be those employed in that communication, namely:

M waves—muscle action potentials evoked by primary excitation of motor fibres;

F waves—muscle action potentials of reflex origin, subserved by afferent fibres of slower conduction than motor fibres in the same nerve segment;

H waves—action potentials elicited most readily in calf muscles through the intermediary of a stretch reflex arc;

Late waves—repetitive muscle action potentials of uncertain nature;

Sensory nerve action potentials.

1. *M waves and Motor Nerve Fibres*

Figure 1 illustrates the findings when hypothenar muscle action potentials were recorded successively at intervals during a forty six minute period of ischemia. The records of the left hand column were obtained following stimulation of the ulnar nerve behind the elbow, about 8 centimetres distal to the lower border of the occluding cuff. The records on the right show the result when the same nerve was stimulated in the lower forearm. During the course of the experiment, the two sites were stimulated alternately, and at regular intervals, with shocks which were always well above maximal for the nerve.

With the more proximal stimulation, which was nevertheless below the level of the cuff, it is apparent from the left hand column that the latency of the M waves (presumably due mainly to motor nerve conduction time) became progressively greater during the period of

circulatory arrest. An increase of about 5 milliseconds had occurred after thirty four minutes of ischemia. Furthermore, the M waves, initially unchanged while the latency was beginning to increase in the

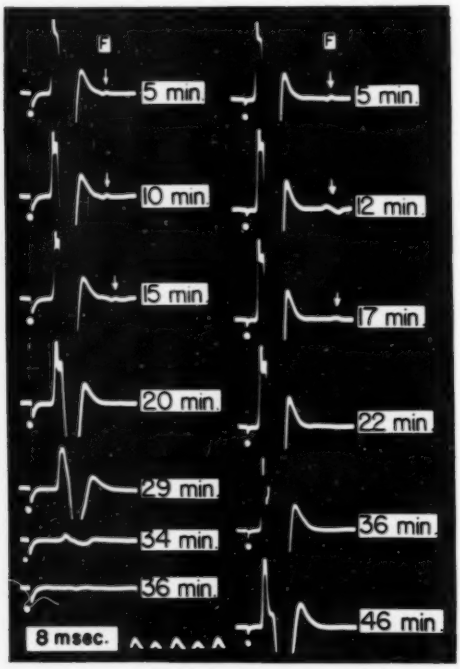

FIG. 1. Action potentials from hypothenar muscles following single maximal shocks to ulnar nerve. Surface electrodes. Left column—stimulation at elbow—conduction distance 30.5 cm.. Right column—stimulation at wrist—conduction distance 8.5 cm.. Pressure cuff upper arm inflated to 200 mm. Hg. before first records. Duration of ischemia prior to each tracing is shown. Amplitude of initial M waves—6 mV.

upper four records, later became simplified in form and then decayed rapidly to virtual extinction.

Similar changes occurred in response to stimulation in the lower forearm (right hand column). They were, however, later in onset and much less marked in degree. A comparison of the records in the left

and right hand columns taken after twenty and twenty two minutes respectively of ischemia, shows a perceptibly increased latency in the former, but none in the latter. Nevertheless subsequent records show, that though later in appearance, slowing did eventually occur with distal stimulation. This was, in the bottom record of the column, of the order of 2 milliseconds. Likewise, decay in amplitude of the M wave, which was very striking with stimulation at the elbow, was much later in appearance when the lower site was stimulated. Only after a full forty six minutes of circulatory arrest was there a diminution of approximately 20 per cent. Occlusion was not maintained long enough to abolish completely the response to this more distal stimulation.

It is clear, therefore, that the same motor fibres in the ulnar nerve trunk which innervate hypothenar muscles, are affected differently in their upper and lower portions in the forearm by this means of producing circulatory arrest. Whereas conduction in distal segments of the pathway is eventually depressed, this depression takes place more rapidly and completely in the proximal parts. Furthermore, a gradient in this mechanism is suggested by the fact that when shocks were applied repeatedly at several intermediate points along the course of the nerve trunk, failure of effective stimulation always occurred in succession from proximal to distal site.

2. *F Waves and Certain Afferent Nerve Fibres*

Close examination of the early records of Figure 1 reveals the presence of F waves, already shown to be reflex in origin (Magladery and McDougal, 1950). For more vivid demonstration, the records of Figure 2, taken from the same experiment, show them with higher amplification. The right hand column illustrates the results of distal, the left hand column those of proximal, stimulation of the ulnar nerve. F waves have been labelled and indicated with arrows in the upper records of each column. The M wave excursions went completely off the face of the cathode ray tube and their configuration was distorted. However, the initial upstroke is clearly seen and was used for latency measurements. The changed latencies of the F waves, contrasting in direction to those of the M deflections, are evident when stimulation occurred at widely separated points over the ulnar nerve (Magladery and McDougal, 1950).

During relatively early stages of ischemia, with either site of stimulation, the latency of the F wave, as can be seen in the sequence of records in the two columns, increased progressively. With shocks at the elbow, however, the delay was of less magnitude, about 4 milliseconds after twenty minutes of ischemia, than with stimulation in the lower forearm where a corresponding figure of about 6 milliseconds was obtained. The increasingly delayed F waves dwindled in amplitude, were found less constantly, and finally disappeared. Extinction oc-

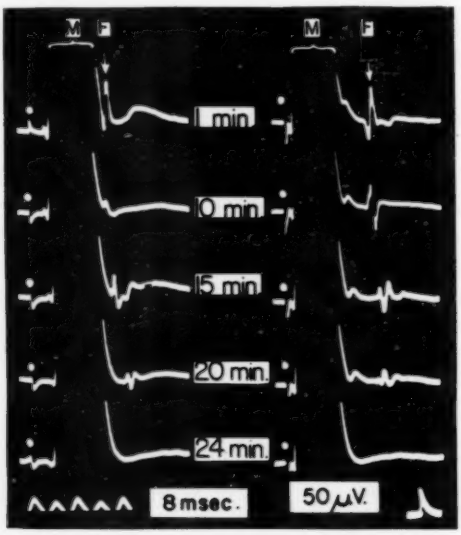

FIG. 2. (Same experiment as that of Figure 1—higher amplification). Details as in preceding legend. Calibration—50 microvolts.

curred in this experiment at a time when the M waves were delayed by only about 1 millisecond with stimulation at the elbow, and were not measurably delayed with distal shocks. Examination of the records of Figure 1 shows that there were, at this time of extinction of F reflexes, minimal changes in amplitude and configuration of the M deflections with proximal stimulation, and none when the stimulus was applied at the distal site.

The magnitude of the delays of the M and F waves varied from

subject to subject and apparently depended, to some extent, on the duration of ischemia. In two other experiments similar to that just described, the latencies of the F waves evoked by stimulation at proximal and distal sites had increased by 3 and 4 milliseconds, respectively, before the deflections were finally abolished. In these cases, no increase in latency of the M wave which followed stimulation at the elbow could be detected. In yet two other instances, the delays of the F waves were 5 milliseconds with stimulation at the proximal site and 8 milliseconds following distal shocks. In these last experiments, the latency of the M waves had increased by 2 milliseconds before F deflections disappeared from the records.

The greater delay of F waves with distal than with proximal stimulation indicates a slowing of conduction, well distal to the occluding cuff, in afferent fibres subserving the reflex. In the experiment illustrated by Figures 1 and 2 these fibres were found, prior to occlusion, to conduct at 55 metres per second in this region (cf. Magladery and McDougal, 1950). In the late stages of ischemia their velocity dropped to 36 metres per second or less. Conduction in motor fibres which initiate the M waves was not slowed to the same degree. From an initial velocity of 68 metres per second it decreased only to 56 metres per second. Thus these motor axones seem to be less sensitive to depression by ischemia than are the afferent fibres subserving the F reflex. This is confirmed by their ability to conduct impulses at a time when the F reflex had been abolished. In this comparison, the more rapidly conducting fibres were found to be the less readily depressed by ischemia. This is in contrast to the relative susceptibilities of portions of motor axones conducting at different rates described above, where a reverse relationship was found.

A greater part of the delay during ischemia of the F waves was found, however, equally with stimulation at two widely separated points. This could only occur in either afferent fibres between the proximal site of stimulation and upper border of the cuff, or the motor limb of the reflex arc below the highest level of occlusion. The relative contributions of these two pathways could not be determined in the above observations. They were evaluated, however, in other experiments with the cuff placed around the upper forearm, thus permitting stimulation of the ulnar nerve above the occlusion. With such stimula-

tion the effects of ischemia were limited to the motor side of the reflex arc at, and distal to, the cuff. It was then found (Figure 3) that neither M nor F waves were measurably delayed during the first fifteen minutes of ischemia; after thirty minutes they were both delayed and equally, but only by about 4 milliseconds. This small delay in total F reflex time may be compared with much greater delays found when the

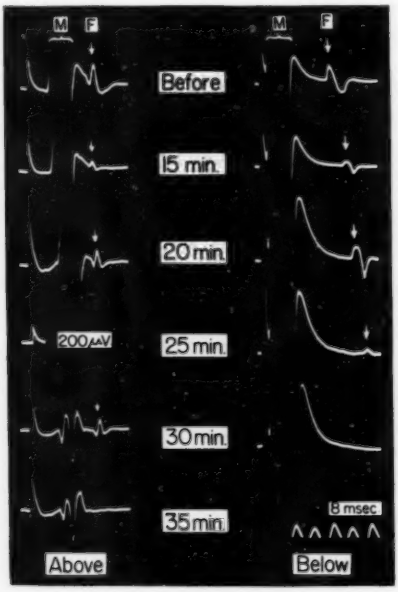

FIG. 3. Action potentials from hypothenar muscles. Surface electrodes. Single maximal shocks to ulnar nerve above (left hand column) and below (right hand column) pressure cuff around upper part of forearm. Upper records—before occlusion. Remaining records 15, 20, 25, 30, and 35 minutes after cuff inflated to 200 mm. Hg.. Prominent deflection of stimulus artefact seen in all records.

nerve was stimulated below the cuff. From that site the F waves were delayed by 7 milliseconds as soon as fifteen minutes after the beginning of occlusion, at a time when there was no increase in latency following stimulation above the cuff. This whole delay must, therefore, have taken place in afferent fibres between the two sets of stimulating electrodes. As ischemia continued there was no marked further slowing of

afferent conduction. The additional latency increase—an extra 5 milliseconds—could be mainly accounted for by the 4 millisecond increase which had, by this time, developed on the motor side.

The accumulated results of the effects of ischemia indicate, therefore, that early progressive delays in the appearance of the F waves are due to decreased conduction velocity in the afferent fibres of the reflex, and that this takes place for the most part in the most proximal segments of those fibres. This deduction has been made, however, on the basis of evidence that the delays occurred at an early stage of ischemia when velocities of single impulses in motor fibres were unchanged. The potential changes in the muscle itself indicating the F reflex are initiated ultimately by a second volley of impulses which travel distally in motor fibres at certain intervals after the original motor volley. The intervals depend on the site at which the nerve trunk is stimulated. They were never, in these experiments, less than 15 milliseconds. It seemed possible that this time might not be adequate, under conditions of ischemia, for recovery of motor axones or myoneural junctions before the arrival of a second volley and that part, at least, of the F wave delay might rest on such a basis. In order, therefore, to test the ability of nerve, myoneural junction, and muscle to respond to repeated nerve volleys, the initial shocks to the ulnar nerve above the occluding cuff were followed by second stimuli at various intervals. The records of Figure 4 illustrate the findings in one of two such experiments on different subjects. The left hand column shows records obtained with two maximal nerve stimuli at the beginning of the experiment, before cuff occlusion. The stimulus interval varied from 5 to 18 milliseconds. The middle column contains records evoked by single maximal stimuli at different times during the course of ischemia. It can be seen in the lowest record of that column, taken after twenty five minutes of occlusion, that the deflection of the F reflex was no longer present. Three minutes afterwards, the records on the right were obtained. Double shocks, of intensity maximal for the nerve, were separated by intervals roughly comparable to those used at the beginning of the experiment. A comparison of records in the right and left hand columns shows that the amplitude and latency of the M wave evoked by the second stimulus, except where deflections overlap, were essentially the same as those produced by the first shock,

both at the beginning of the experiment and also after the period of ischemia necessary to abolish the deflections of the F reflex. In other experiments, with shorter periods of ischemia, submaximal shocks were employed as second stimuli. The results were the same. It seems clear, therefore, that F wave delays could not be attributed to slowed recovery of ischemic motor axones, myoneural junctions, or muscle. On the contrary, deductions made above on the basis of single stimuli seem well justified—namely, that early delays in the F deflections

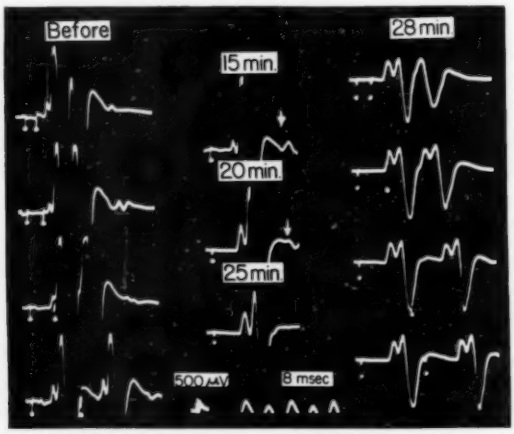

FIG. 4. Action potentials from hypothenar muscles. Surface electrodes. Stimulation to ulnar nerve by maximal shocks above pressure cuff around upper forearm. Left hand column shows results of double shocks at various intervals before occlusion. Middle column shows, from above downwards, records evoked by single shocks 15, 20, and 25 minutes after cuff inflated to 200 mm. Hg.. Right hand column shows results of double shocks 28 minutes after occlusion. Stimulus artefacts marked by dots.

evoked in an ischemic limb are due to decreased conduction velocity in afferent fibres of the reflex arc. This evidence, in conjunction with velocity differences, has already been used in establishing the fact that the pathway to the spinal cord of impulses subserving F waves is along afferent, rather than motor, fibres and that these deflections represent a true reflex response (Magladery and McDougal, 1950).

The present results also indicate that certain afferent fibres, in this case those subserving the F reflex, are affected by circulatory arrest

sooner, but nevertheless in the same fashion as motor fibres. Both groups are depressed to some extent throughout their whole course in the ischemic portion of the limb. The depressant effect is, however, much more rapid in onset in more proximal segments, regions where

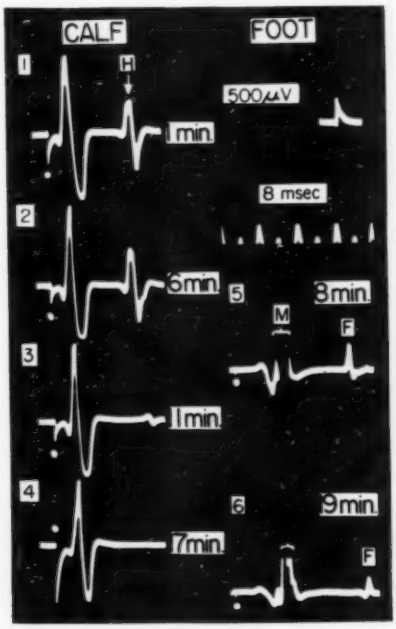

FIG. 5. Muscle action potentials. Surface electrodes. Shocks to posterior tibial nerve in popliteal fossa. Records 1 to 4—deflections from calf muscles following submaximal stimulation. Records 5 and 6—deflections from small foot muscles following maximal stimulation. Times of tracings after inflation of thigh pressure cuff to 200 mm. Hg. shown in figure.

normally conduction rates are greater than those found distally in both motor and afferent fibres (Magladery and McDougal, 1950).

3. H Waves and their Afferent Fibres.

Records 1 to 4 of Figure 5 illustrate action potentials recorded through surface electrodes from calf muscles following submaximal stimulation of the posterior tibial nerve in the popliteal fossa. The M

wave of the first record was followed by the prominent H wave which is characteristic of this stretch reflex (Hoffmann, 1922), (Magladery and McDougal, 1950). Records 5 and 6 show deflections led from small foot muscles following stimulation at the same popliteal site with shocks which were well above maximal for the nerve. The duration of circulatory arrest applying to each record is shown in the figure.

From records 1 to 3 it is seen that during relatively early stages of ischemia, the H wave became progressively later and soon dwindled rapidly in amplitude. A delay of 8 milliseconds had occurred after eleven minutes of occlusion. Shortly thereafter the H reflex deflections had been abolished. At this point ankle jerks, previously obtainable, could no longer be elicited, in confirmation of Hoffmann's (1922) original identification of this deflection with the tendon reflex. Power was virtually normal. It is apparent from the records that the M wave and its latency were relatively unchanged at this time.

Extinction after such short periods of ischemia have not been noted with F reflexes found in hypothenar muscles following ulnar nerve stimulation. This fact, in itself, accentuates further the difference between the two reflexes. F waves usually persist, though showing progressive delay, for twenty or twenty five minutes. Figure 5 shows that this degree of resistance to depression during circulatory arrest obtains also for F reflexes in small foot muscles. It has not yet been found possible to stimulate effectively the posterior tibial nerve proximal to the occluding cuff. It cannot, therefore, be shown directly that the delay and eventual extinction of the H reflex during this short period of ischemia occurred in its afferent limb. Nevertheless, afferent fibres subserving F reflexes persisted during many more minutes of occlusion than the H deflections, and the former have already been shown in the upper limb to be even more readily depressed by ischemia than motor fibres. It seems justifiable, therefore, to assume that the H reflexes were abolished at a time when motor fibres in the lower thigh, of velocity similar to those in the arm, were relatively unaffected. This early depression of afferent fibres already shown (Magladery and McDougal, 1950) to be of high conduction velocity is in agreement with the observation that afferent fibres of F reflexes are first affected in proximal segments where impulses are normally conducted more rapidly than in distal regions of the nerve.

4. *Late Waves.*

Late waves (Magladery and McDougal, 1950) are, like H reflexes, very susceptible to the effects of circulatory arrest. In Figure 6 action potentials from hypothenar muscles were recorded continuously on moving paper. The records in sequence show the results of continuing ischemia on the composite pattern. It is apparent that the M waves were relatively unchanged throughout this length of time, indicating

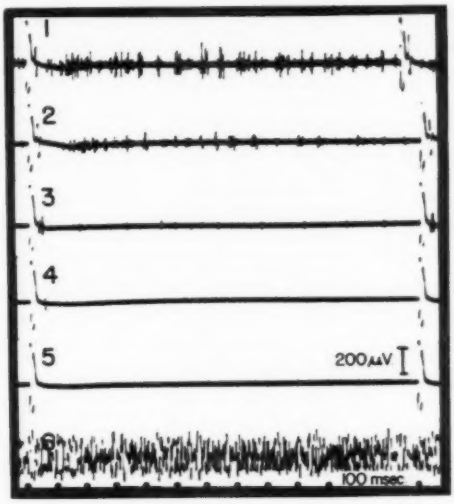

FIG. 6. Action potentials from hypothenar muscles following single maximal shocks to ulnar nerve in forearm. Surface electrodes. Continuous recording. Record 1—before ischemia. Records 2 to 5—12, 22, 32, and 36 minutes respectively, after cuff inflation upper arm to 200 mm. Hg.. Record 6—action potentials accompanying voluntary movement at time of record 5. Dot indicates F wave.

a normal activity in distal portions of the motor pathway. There was some loss of voluntary power, but the final record of the figure shows action potentials accompanying voluntary effort which were comparable to those seen in the presence of normal circulation.

Closer scrutiny of Figure 6 likewise reveals the sequence of delay and extinction of F reflexes to which reference has been made in an earlier section. More evident, however, is an early decay of the late waves.

After only twelve minutes of ischemia they had diminished in number, amplitude, and duration. After twenty two minutes (record 3) they had virtually disappeared. It is of interest to note in that record the apparently rhythmic beating of the much reduced activity before final extinction. Subsequent records show no trace of late waves, although deflections of the F reflex, diminished and delayed it is true, were still present for several more minutes.

The significance of late waves still lacks interpretation. In a previous paper, attention was drawn to the repetitive nature of the usual pattern, and to the resemblance of this to the type of response in animals elicited by stimulation of the pyramidal region (Skoglund, 1947) or from continued slight stretch of muscle (Bernhard and Therman, 1947). This feature is even more evident, as just seen, when the number of units contributing has been reduced by ischemia. It has not yet been conclusively proven that late waves are reflex in origin. Likewise, it has been impossible to determine velocities in the fibres responsible for them. It may be pointed out, nevertheless, that the marked decrease in amplitude and frequency of the discharges seen in the early records of Figure 6 occurred at a stage of ischemia at which the authors have never encountered depression of conduction in motor fibres. This indicates that little, if any, of the pattern was blocked in the peripheral motor pathway. There is no evidence in man to indicate whether or not depression of sensory endings takes place during a brief period of circulatory arrest, although Matthews (1933) found in cats that certain muscle end organs, or terminal afferent fibres, became inexcitable with very short periods of limb ischemia. It has, however, just been shown in this paper that afferent fibres of high conduction velocity subserving the stretch reflexes of Hoffmann (1922) undergo marked slowing and block during similarly brief periods of ischemia as those which depress late waves. This may suggest that if these late waves are, in fact, reflex in origin, they may also be subserved by rapidly conducting afferent pathways. If this is so, it would be somewhat against a surmise that they represent repetitive discharges of the nature of F reflexes, though such might well be the case. On the other hand, their sensitivity to the effects of ischemia might even prompt speculation that, in those regions where H waves are not found, the asynchronous pattern appears as a counterpart.

5. *Sensory Nerve Action Potentials.*

A similar sequence of slowing, diminution in amplitude, and eventual extinction was seen when nerve action potentials were recorded during ischemia. The records of Figure 7 were taken at intervals during an experiment in which the sphygmomanometer cuff was placed around the upper part of the forearm. The ulnar nerve was stimulated in the

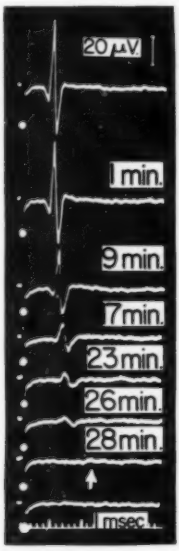

FIG. 7. Nerve action potentials following maximal single shocks to ulnar nerve in low forearm. Surface recording over ulnar nerve above elbow. Pressure cuff upper forearm inflated to 200 mm. Hg.. Record 1—before ischemia. Subsequent records—1, 9, 17, 23, 26, 28, 33 minutes after onset of ischemia. Time—1 and 5 msec.

lower forearm. Sensory nerve action potentials (Dawson and Scott, 1949) were recorded from the same nerve trunk above the elbow, proximal to the cuff. Essentially comparable results have been obtained in other experiments in which occlusion was effected central to the recording electrodes. It is apparent from the records of Figure 7 that increased latency and decreased amplitude of the deflection was found

within the first few minutes of ischemia. After seventeen minutes, the much reduced deflection was delayed by about 2 milliseconds. Occlusion of this duration had little effect on conduction in motor fibres (Figure 1). Voluntary power was still relatively normal. Recognition, however, of all forms of sensory stimuli except those producing "deep" pain was diminished to some extent. With this one exception, no subject was able to report progressive impairment of any one sensory modality disproportionate to, or to the exclusion of, another.

The remaining records of Figure 7 show progressive slowing and diminution in deflection size. When latencies and amplitudes were plotted against duration of ischemia, there was no break in the resultant smooth curve obtained. It would seem reasonable to assume that this implies a progressive depression and block in the same fibres which initially conducted impulses of high velocity represented by the sharp action potentials of the upper records. This may well be the case. In the present experiment, however, impairment in recognition of all sensory stimuli became profound by the time that the nerve deflection was finally extinguished after twenty eight minutes of occlusion. There is abundant evidence to suggest that impulses associated with various forms of sensation are carried centrally in fibres which differ over quite a range in conduction velocity (Gasser, 1935, 1942). Under these conditions of prolonged ischemia, therefore, the deflection may well indicate activity in other than the most rapidly conducting afferent fibres. This last interpretation of the changes in the nerve action potentials during limb occlusion would not, however, explain why contributions of impulses in fibres of slower conduction velocity do not appear commonly after the sharp spike in the normal state. Dawson and Scott (1949) mention instances where later deflections were occasionally found with exceedingly strong stimuli. Sometimes in the present studies, a second wave has been encountered (Figure 10 in the preceding communication). Usually, however as in the experiment illustrated by Figure 7 of this paper, there is only one deflection. It is possible that in such cases dispersion of slowly conducted impulses is too great to allow a wave formation. It may be that ischemia, which has its greatest depressant effect on more rapidly conducting afferent fibres, creates by this means a more synchronous volley in the more slowly conducting group.

When action potentials were recorded alternately from hypothenar muscles and nerve during the course of the same experiment, certain relationships appeared. These were comparable to those which may be made by comparing Figure 7 with the records of Figures 2 and 6. Late waves from muscle disappeared at the time when the nerve action potential was much reduced in amplitude and some impairment in recognition of sensory stimuli was apparent. Final extinction of the deflection in the nerve records, however, only took place at about the same time that F reflexes were abolished and sensory impairment was profound. These comparative findings are compatible with the proposal that the long-persisting elevation in the nerve action potential may represent activity, under these ischemic conditions, in fibres other than those of the greatest conduction velocity.

The effect of occlusion on sensory nerve action potentials is not restricted to the region of the pressure cuff. It can be shown just as readily with the cuff high in the arm, as when it is placed around the forearm. As with motor fibres, the effect is a general one throughout the length of sensory nerve involved. Due to limitations in feasible sites of recording nerve deflections, it has not been possible to measure directly the relative effects of ischemia on proximal and distal stretches of the afferent fibres contributing to the nerve action potential. A disproportionate effect has, however, been demonstrated by indirect means. When the occluding cuff was placed high in the arm, the nerve could be stimulated at several different points in the forearm, and latencies determined over increasingly longer segments of afferent fibres distal to the recording electrodes. Under such conditions it was found that during early stages of ischemia the latency increased to the same extent in all segments. This can only mean that the decrease in velocity must have occurred in that region of nerve proximal to the highest point of stimulation. By exclusion it can be inferred that more distal nerve segments were resistant to depression by this degree of ischemia. Impulses in afferent fibres indicated by nerve action potentials are, then, delayed more quickly by ischemia in their proximal, more rapidly conducting, regions than distally where normally conduction velocity is less.

This relationship, therefore, of greater sensitivity to ischemic depression in the proximal and more rapidly conducting portions of the same

fibres in mixed nerve trunks, has been found to obtain for motor axones and for afferent fibres of different conduction velocities. However, as can be seen in Table 1, which is presented in summary, sensitivity to ischemia does not run completely parallel to conduction rate when different types of fibre are compared with one another. In all three instances where afferent fibres were studied, sensitivity to the effects of occlusion increased with increasing conduction velocity. Motor axones, however, though normally conducting more quickly than afferent fibres of F reflexes, were found to be more resistant than the latter.

TABLE I

Conduction Velocity of Nerve Fibres and Relative Sensitivity to Ischemia

CONDUCTION VELOCITY (decreasing order)	SENSITIVITY TO ISCHEMIA (decreasing order)
1. Afferent Fibres of —H Reflexes (popliteal fossa) —Nerve Action Potentials (forearm, popliteal fossa)	1. Afferent Fibres of —H Reflexes (popliteal fossa) —Nerve Action Potentials (forearm, popliteal fossa)
2. Motor Nerve Fibres (forearm, popliteal fossa)	2. Afferent Fibres of F Reflexes (forearm)
3. Afferent Fibres of F Reflexes (forearm)	3. Motor Nerve Fibres (forearm, popliteal fossa)

DISCUSSION

It has been the purpose of this paper to consider the effects of ischemia, as produced by sphygmomanometer cuff pressure, on certain objective results evoked by stimulating low-threshold, presumably Group A, fibres in mixed peripheral nerve trunks in man. Essentially similar results have been obtained under different sets of circumstances. It has been shown that depression caused in this fashion is shared by motor fibres, by rapidly conducting afferent fibres of H stretch reflexes, by more slowly conducting fibres of the afferent limb of F reflexes, and by centrally conducting fibres indicated by sensory nerve action potentials. Furthermore, it has been possible to show for three of these, namely motor axones, afferent fibres of the nerve action potential, and those subserving F reflexes, that this depression is a generalized one affecting both proximal and distal segments of the nerve trunk. It is apparent, therefore, that the effects of circulatory

arrest produced by this means must act over great stretches of nerve trunk, and not be restricted to the segment directly underlying the cuff.

It has also, however, been shown in the present communication that the depressant effects of cuff occlusion appear earliest and most profoundly in the proximal portions of mixed nerve trunks long before distal regions are affected. This was found true not only for motor axones, but also for more rapidly conducting afferent fibres contributing to the nerve action potentials, and more slowly conducting afferent limbs of F reflexes. Interpretation of the different rate and magnitude of this depressant effect on upper and lower portions of fibres must, then, be included in any explanation of the effects of ischemia. It was suggested by Weddell and Sinclair (1947) that direct pressure by the cuff over the underlying segment of nerve trunk led to the sensory changes following cuff occlusion. It is quite conceivable that this mechanism may, in fact, play a part in the finding that sensory changes usually appear first in the distribution of a specific nerve, and that the long extensor of the thumb is often affected early. However, it cannot readily explain the predominant general proximal spread of paralysis nor the depression of conduction and excitability which has been demonstrated to exist in both afferent and motor fibres for many centimetres below the occluding cuff, and eventually throughout the whole ulnar nerve trunk.

Under these conditions of circulatory arrest in the whole distal part of the limb, it seems reasonable to attribute the depression to the effects of anoxia. This interpretation has, moreover, support from studies of the effect of oxygen lack on nerve fibres in experimental animals. Hertz (1947) found that depressant effects of anoxia occurred in proximal segments of frog single fibre preparations in about half the time taken for distal portions to be involved. Groat and Koenig (1946) likewise found that asphyxia in cats was accompanied by depression of motor nerve excitability which spread centrifugally. These results are completely analogous to those just described in man, and suggest a common mechanism. Anoxia of the whole limb, both underneath and distal to the occluding cuff, could very well produce the results presented in this communication.

In a previous paper (Magladery and McDougal, 1950) it was shown that a peripheral slowing in conduction obtained in man for both

afferent and motor fibres in the ulnar nerve trunk. The present paper has demonstrated that in both afferent and motor fibres again, cuff occlusion or, as has just been suggested, anoxia, produces its earliest and greatest depression on proximal segments and that subsequently there is a distally moving depressant action. Apparently then, there are two characteristics, namely velocity of conducted impulses and sensitivity to oxygen deprivation, in which both motor and afferent nerve fibres, in man at least, manifest a gradient. It is a gradient between proximal, more rapidly conducting regions which are most sensitive to anoxia, and more slowly conducting and resistant distal segments.

It has also been shown that the effects of ischemia on different classes of fibre in mixed nerve trunks in man are produced at diverse rates. It seems clear that those of the afferent limb of H reflexes, and those contributing to the most rapidly conducted components of sensory nerve action potentials, are depressed early. Afferent fibres of F reflexes are next affected in order of time. In all three cases, therefore, where centrally conducting fibres were studied, sensitivity to the effects of ischemia was found greater with increased conduction velocity. Motor fibres, however, already shown to conduct more rapidly than afferent fibres of F reflexes, were found to be more resistant than the latter to this depression. A completely satisfactory explanation of this apparent exception is not forthcoming.

Gasser (1935) (1942) and others who have attempted to correlate conduction rates in the experimental animal with relative sensitivities to ischemia, have encountered somewhat similar difficulties in interpretation. There seem to be at least two possible explanations for the results which we have obtained. One would be that there is no parallel relationship between conduction rates and sensitivity to ischemia in different groups of fibres. This interpretation is difficult to reconcile with observations just presented which indicate that in the same fibres conduction velocities and sensitivity show some parallelism. An alternative explanation would suggest that there is something inherently different between afferent and motor fibres in the same nerve trunk, whereby the former are more sensitive to oxygen lack regardless of relative conduction rates. Such a difference, perhaps in some metabolic feature, between afferent and motor fibres would not be too surprising. Lehman (1937) has already shown in cats that alterations in

after-potentials which accompany asphyxia are quite different between sensory nerves on the one hand, and mixed and motor nerves on the other. Skoglund (1942) has indicated another difference, also in cats, by showing that accommodation is much more rapid in motor than in sensory fibres. An interpretation based on inherent differences between these two broad groups would imply that, within either group, the more rapidly conducting fibres are relatively more sensitive to anoxia than those of slower conduction velocity. Gasser (1935) found in the cat that of sensory Group A fibres the most rapidly conducting members were eliminated first by ischemia. These were followed, soon afterwards, by fibres which were considerably slower in conduction. Only later were those of an intermediate conduction velocity affected. It may well be that in man we have a counterpart of this situation with the A group, and that motor fibres are in some way analogous of the intermediate, more resistant afferent sub-group which Gasser encountered in his animal studies.

SUMMARY

Ischemia, produced by limb occlusion with a sphygmomanometer cuff, has a depressant effect on conduction in Group A motor and afferent fibres in peripheral nerve trunks in man. This effect is a generalized one throughout the fibres, and not the result of local pressure on the segment directly underlying the occluding cuff.

In representative groups of both afferent and motor fibres depression occurs earlier, and is more profound, in proximal than in distal parts of the same nerve fibres. This finding, taken in conjunction with comparative conduction velocities, suggests that a gradient exists for these characteristics throughout the nerve trunks.

In all three instances where afferent fibres were studied, sensitivity to the effects of ischemia increased with increasing conduction velocity. Motor fibres, however, were somewhat more resistant than certain afferent fibres of slower conduction rate.

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ELECTROPHYSIOLOGICAL STUDIES OF NERVE AND REFLEX ACTIVITY IN NORMAL MAN

III. The Post-Ischemic State[1]

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The release of an otherwise normal limb from circulatory arrest is followed by a variety of sensory and motor changes. Reid (1931) described such paraesthesiae and correlated them temporally with motor responses in distal muscle groups. He reported the latter in detail as "fibrillary twitchings" and stated "especially during its later part, the contractions become markedly prolonged" (Reid, 1929). His deductions that these phenomena arose from a hypocalcemic hyperexcitability of peripheral sensory endings and muscle fibres lack adequate support. Nonetheless, his observations merit careful attention.

Almost concurrently, Lewis, Pickering, and Rothschild (1931) studied the symptoms and signs accompanying prolonged ischemia and its release. These were reported in detail, in some respects differing from those noted by previous observers. They found that the return of circulation to a limb was accompanied by sensations of tingling and of tightness. The latter were termed "pseudocramp" in apparent denial of a motor component. The findings and interpretations of these authors have met wide acceptance until recently.

Weddell and Sinclair (1947) repeated many of the earlier experiments dealing with the clinical aspects accompanying ischemia and following its release. Many features of the paraesthesiae on release were found to differ from those appearing with occlusion. Furthermore, on the basis of experience with amputees, release paraesthesiae, in contradiction to Lewis, Pickering, and Rothschild (1931), were considered to take origin distally at actual pain nerve endings. The

[1] These investigations have been supported financially, for the most part, by the Lewis J. and Harriet S. Lederer Fund of the Johns Hopkins University.

mechanism of activation was thought related to the presence of metabolites.

More recently, Merrington and Nathan (1949) have reported the results of numerous experiments on themselves and on patients with different lesions of peripheral nerves and central nervous system. The studies were confined to post-ischemic paraesthesiae. These were described in detail and the time course of various subjective components compared. Results from ingenious procedures led to conclusions that the impulses felt as paraesthesiae arose in nerves, rather than endorgans, and that the fibres concerned were those which normally subserve sensations of touch, pressure, and movement.

These conflicting descriptions and conclusions from the most recent observers indicate the desirability of further study. This has been attempted in the present investigation wherein objective recording methods were applied to certain characteristic features which follow release from ischemia. The findings will be interpreted, wherever possible, in the light of alterations found to be produced during the post ischemic state in evoked action potentials of muscle and nerve (Magladery and McDougal, 1950).

PROCEDURE

The experimental arrangement for recording action potentials and for stimulation has been described in a previous paper (Magladery and McDougal, 1950). All experiments entailing a recognition of subjective sensations were performed, at least once, on the authors of this paper. Ischemia was effected by the use of an ordinary sphygmomanometer cuff. Unless stated otherwise, the cuff, 12 centimetres in width, was applied around the arm with its distal border about 8 centimetres above the crease in the antecubital region or around the lower thigh. Pressure was maintained at 200 mm. Hg for about thirty minutes or until voluntary power in distal muscles was completely lost. It was then rapidly released. Sensory experiences of the subject, and their relationships in time, were recorded. Frequent notes were made of muscle movements and consistency.

Intraneural procaine blocks, when used, were to the ulnar and median nerves at the level of the elbow. Four or five cc. of two per cent procaine with epinephrine were used with each block. Intra-arterial injections were made through an indwelling cannula in the brachial artery in the cubital fossa.

All sites of block, stimulation, and recording were marked and measured in relationship to a fixed point at the conclusion of each experiment.

RESULTS AND INTERPRETATIONS

A. *Spontaneous Activity*

The sensory experiences which appear after the release from a prolonged period of ischemia have been described by Reid (1931), Lewis, Pickering, and Rothschild (1931), Weddell and Sinclair (1947), Merrington and Nathan (1949), and others. The temporal relationships of such paraesthesiae have been especially stressed by Merrington and Nathan (1949). All have described these subjective experiences at length and drawn sharp differentiations between qualities. In the present study, there has been no attempt to make these fine distinctions. The general features were much as follows.

Soon after release of the occluding cuff there was a dramatic flush throughout the limb distal to it. This was soon followed by a short-lived pleasant diffuse feeling of warmth throughout the same distribution. This phenomenon of reactive hyperemia has long been recognized (Lewis and Grant, 1925), (Eichna and Wilkins, 1941), (Weddell and Sinclair, 1947). The color changes are well shown photographically in the paper of the last-named authors.

About forty-five seconds or a minute after restoration of circulation, characteristic paraesthesiae began to make their appearance. At first, these consisted of scattered stinging sensations which felt, to some observers, as though they were being appreciated in superficial tissues of the fingers and hand. They increased rapidly in intensity, frequency, and area of distribution. They were usually most intense about thirty seconds or a minute after the onset, remained so for perhaps a minute, then declined over yet another minute or two. A few vestiges sometimes persisted for many minutes.

Not long after the onset of the stinging sensations, a quite different feeling of tightness was experienced in the depths of the hand and soon afterwards in the forearm. This, too, became increasingly intense over the next minute or so until a maximum was reached. At such a time it was described as quite unpleasant by most subjects. Subsequently it, in turn, declined and disappeared after a very few minutes. For purposes of description this paraesthesia, to which we shall direct most attention, will be called "tightness".

Accompanying the onset of the feeling of tightness, motor changes were evident in the distal portion of the limb. These varied from palpable hardness of the muscles in some subjects to gross changes of posture in others. These motor phenomena, hereafter referred to as "spasm", increased, like the feeling of tightness, to a maximum, then slowly declined over a minute or two. In subjects who showed most marked motor responses, a fairly constant pattern was followed. There was first a visible contraction of muscles in the thenar and hypothenar eminences. The hand was progressively drawn into a cupped position and then usually pulled slowly backwards in dorsiflexion at the wrist, and maintained in that position until the maximal intensity had

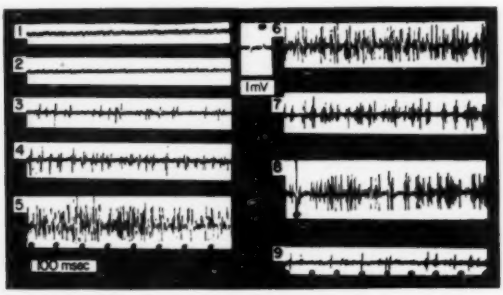

FIG. 1. Action potentials from hypothenar muscles. Continuous recording Surface electrodes. Cuff upper arm released after 30 minutes at 200 mm. Hg Records taken successively 5, 30, 45, 60, 75, 90, 105, 120, 150 seconds after release. In record 8 the dot indicates a single maximal shock applied to ulnar nerve.

passed. When the electrical activity accompanying this motor response was recorded on continuously moving paper, a characteristic picture was seen. The records of Figure 1 are taken from such an experiment. Record 3, made one minute after cuff release, shows the early appearance of scattered bursts of action potentials. The succeeding three records, taken at fifteen second intervals, show the progressive development of this activity to a continuous pattern of irregular repetitive muscle discharge of a violent type. This occurred at the height of the subjective feeling of tightness and visible spasm of the limb. Records 7 and 9 portray the progressive decline of electrical activity as the phenomenon wore off.

It is apparent, therefore, that restoration of circulation to a pre-

viously ischemic limb is accompanied not only by marked paraesthesiae, but also by a concomitant motor response or spasm of varying degrees of intensity. The remaining portions of this paper will be devoted to a study of some of the mechanisms underlying the production of this pattern.

B. *Evoked Responses*

1. *M. and F waves—Repetitive Firing*

For various reasons, including convenience and the relative rates of recovery from ischemia, the upper limb was usually employed in studying the behaviour of these components following restoration of

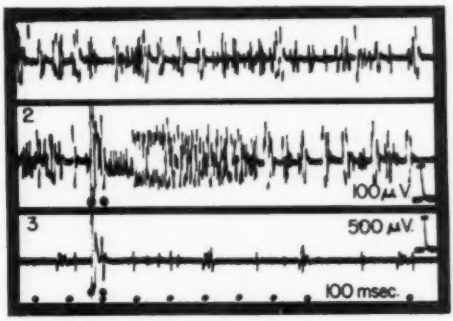

FIG. 2. Action potentials from hypothenar muscles. Surface electrodes. Pressure cuff upper arm released after 37 minutes at 200 mm. Hg. Record 1—1 minute after release. Records 2 and 3—maximal single shock to ulnar nerve in forearm 2½ and 10 minutes, respectively, after release.

circulation. Only when stretch reflexes of Hoffmann (1922) were under investigation was the leg used.

As soon as the tightness appeared, electrical stimulation of the ulnar nerve at the elbow became once more effective. During the intense random activity of the concomitant spasm, however, muscle action potentials induced by nerve stimulation were of decreased amplitude and it was often difficult to detect the early signs of their presence. Record 8 of Figure 1 indicates that they sometimes did little more than accentuate the underlying activity. When the latter began to subside, however, a phenomenon appeared, to which Kugelberg (1946) has already drawn attention. In record 2 of Figure 2, for

example, stimulation of the ulnar nerve in the forearm evoked the usual direct motor deflection, the M wave, and also the reflexly produced F response. This was immediately followed by a chain of rapidly repetitive spikes of smaller, then larger, amplitude. Close scrutiny reveals that some of this repetitive activity took place between the M and F waves.

As the spasm subsided completely, this repetitive response to single stimuli was seen against a more favourable background. In some experi-

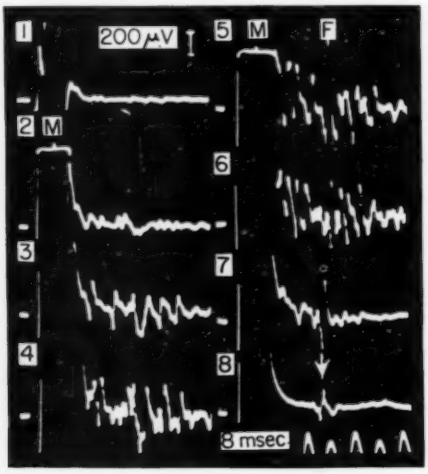

FIG. 3. Action potentials from hypothenar muscles following single maximal shocks to ulnar nerve in forearm. Surface electrodes. Pressure cuff upper arm released after 37 minutes at 200 mm. Hg. Records taken 5, 7, 10, 13, 16, 19, 23, 27 minutes, respectively, after release.

ments, it did not appear until some time after the spontaneous spasm had vanished. In such cases, the conditions conducive to its appearance often continued for many minutes after restoration of circulation. Figure 3 is representative of such experiments. In the first record, the M wave had not yet recovered from its ischemic depression. In record 2, taken seven minutes after release of the occluding cuff, M was virtually normal, but there was no indication of the deflection of the F reflex. In this and succeeding records the growth of the repetitive pattern to a maximum in amplitude and frequency is readily seen.

It will be noted that only after thirteen minutes (record 4), long after return of the M wave to normal, did F waves begin to show in the records. After twenty minutes, repetitive activity was definitely dwindling. Twenty seven minutes after release, nerve stimulation produced no suggestion of the phenomenon and only the accustomed normal picture of the M and F wave relationship was found.

It seems evident, therefore, that the release from ischemia is followed by repetitive discharge of some part or parts of the motor pathway in response to a single nerve stimulus. This repetitive firing has been seen to occur, in some cases, at a time when afferent fibres subserving the F reflex had recovered. In other cases, however, F deflections only reappeared several minutes after the spontaneous spasm had subsided, and the pattern of repetitive discharge of motor components in response to single nerve shocks become well developed. Apparently, in these instances, either recovery had not, at this time, taken place in afferent fibres subserving F reflexes, or central inhibition blocked the motor response normally caused by impulses in these fibres.

2. *Late waves*

Detection of the reappearance of the relatively low amplitude late waves must await subsidence of the post-ischemic spasm and return to a reasonably flat resting baseline. There is no way of knowing, therefore, at what stage return of this activity takes place. Certainly it occurs within a few minutes, and the normal composite picture is then found. Figure 4 is taken from an experiment wherein full late wave activity had recovered six minutes after release of the pressure cuff.

3. *H waves*

The records of Figure 5 were taken at various intervals after release of the leg from thirty minutes of circulatory arrest. Records 1 and 2 show action potentials from calf muscles evoked by submaximal stimulation of the posterior tibial nerve in the popliteal fossa. Within a minute of restoration of circulation, the H wave, which had been obliterated early during the course of ischemia, returned. Within the next minute or so it increased greatly in amplitude to a size far

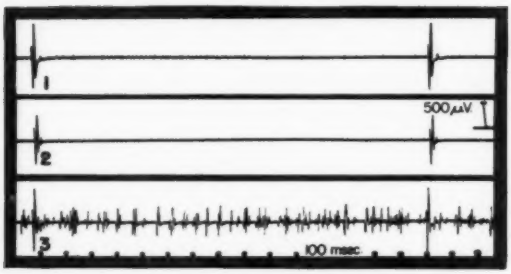

FIG. 4. Action potentials from hypothenar muscles following maximal single shocks to ulnar nerve at elbow. Continuous recording. Surface electrodes. Pressure cuff upper arm released after 34 minutes at 200 mm. Hg. Records 1 and 2 taken after 22 and 30 minutes, respectively, of ischemia. Record 3 taken 6 minutes after release of cuff.

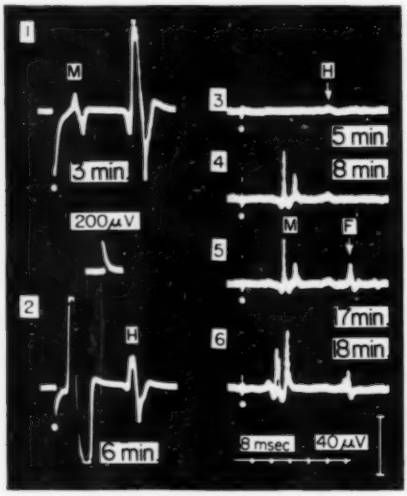

FIG. 5. Muscle action potentials. Surface electrodes. Shocks to posterior tibial nerve in popliteal fossa. Records 1 and 2—deflections from calf muscles following submaximal stimulation. Remainder from small foot muscles following maximal stimulation. Thigh pressure cuff released after 37 minutes at 200 mm. Hg. Records taken at times indicated after release. Calibration at left applied to records 1 and 2. Calibration for remainder shown at right.

exceeding its control value at the beginning of the experiment (Figure 5 of Magladery, McDougal, and Stoll, 1950), despite the fact that the M wave was still depressed.

The reason for this post-ischemic increase in H wave amplitude is not completely clear. It must, at the very least, indicate a return to activity in many afferent fibres at a time when most motor axones were still inexcitable by electrical stimulation. It is conceivable that its increased size may be entirely attributed to such a relationship, although the possibility of additional central facilitation during this period when paraesthesiae were manifest cannot be ruled out. The H reflex potentiation persisted for a fairly brief period of time. Record 2 indicates that six minutes after release from ischemia, motor fibres causing the M waves had recovered and H deflections returned to normal amplitudes.

Records 3 to 6 are those of action potentials from small foot muscles, taken during the same period as those just described, but following stimulation which was well over maximal for the nerve at the same popliteal site. Record 3 shows a diffuse spread of the enhanced H wave from calf muscles, and identified by its latency, at a time when there was no sign of action potentials from the muscles under consideration. There was clearly still depression of motor fibres somewhere between the point of stimulation and foot. The M deflection reappeared, however, within a few minutes (record 4). Finally, after stimulation of the nerve in the popliteal fossa became more effective, F waves made their reappearance in the small foot muscles (record 5). It will be noted that the return of F waves, later than M deflections, occurred only as the spread of H waves from calf disappeared from the records of the foot muscles. Reference to records 1 and 2 indicates that the amplitude of the H wave, itself, had returned at this time to an approximately normal size.

It can be seen, therefore, that restoration of circulation to the lower limb after ischemia is first followed by return of function in the afferent pathways of H reflexes, fibres already shown (Magladery and McDougal, 1950) to be of the highest conduction velocity in the limb. This is followed, in turn, by recovery in motor fibres. As in the upper extremity, F waves reappear last of all.

4. *Sensory Nerve Action Potentials*

The experiment of Figure 6 represents an attempt to detect the onset and follow the time course of recovery of nerve fibres responsible for the action potentials previously described (Dawson and Scott, 1949), (Magladery and McDougal, 1950). Circulation was restored after forty minutes of occlusion which had abolished the deflections (Magladery, McDougal, and Stoll, 1950) and induced loss of all sensation except deep pain.

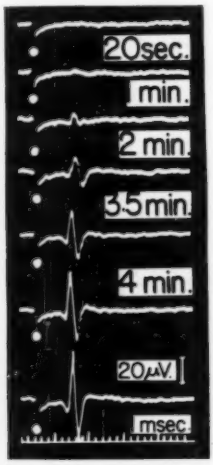

FIG. 6. Nerve action potentials following maximal single shocks to ulnar nerve in low forearm. Surface recording over ulnar nerve above elbow. Pressure cuff around upper part of forearm. Cuff released after 40 minutes at 200 mm. Hg. Record 1 taken during late stages of ischemia. Remaining records taken 20 seconds, 1, 2, 3¼, 4, and 6 minutes after release. Conduction distance—27.5 cm. Time—1 and 5 msec..

Immediately following release of ischemia, maximal stimuli were applied, at one second intervals, to the ulnar nerve in the lower forearm. The usual recording over the nerve above the elbow was used. Every sweep was photographed for the next seven minutes. Notes were made of sensory experiences reported by the subject. As seen in the second record, the first sign of a deflection appeared twenty seconds after release of ischemia. The subject experienced his first sensation of stinging at this instant. The next three records were selected from those

taken during the ensuing three minutes—i.e. during the development, and most intense phase, of the reported tightness and visible spasm. It is apparent that during this period there was a steady increase in amplitude of the action potential and slight decrease in its latency. The last two records of the figure indicate clearly that total recovery, as gauged by this method, did not, however, occur for yet another three minutes. There was no indication, from these records, or similar ones, of the intense asynchronous spontaneous discharge of sensory endings and/or fibres which must have taken place during this period.

When the records of this figure are compared with those of Figure 7 of the preceding paper (Magladery, McDougal, and Stoll, 1950), it is seen that the action potential made its reappearance, after restoration of circulation, with a latency far less than that found during the late stages of its decay during ischemia. The reason for this is not apparent because of uncertainty as to the actual fibres contributing to the normal nerve action potential. Evidence has already been presented (Magladery, McDougal, and Stoll, 1950) implying that impulses in high velocity fibres normally contribute to the major part of it. Nevertheless, persistence of a deflection during later stages of ischemia until many forms of sensation had been abolished, suggested that under those circumstances the deflection may have in addition represented activity in fibres of slower conduction velocity which, under normal circumstances, conveyed impulses too greatly dispersed for detection.

In the present experiment it has been seen (record 2) that the sensory nerve action potential first returned with a latency only 2 milliseconds greater than that found in the normal state (bottom record). This suggests strongly that the sensory fibres which recover first from ischemia are those which normally are the most rapidly conducting. A similar observation in regard to recovery rates of afferent fibres has already been made when it was shown that fibres subserving H reflexes recovered equally promptly.

Evidence has accumulated, therefore, indicating that the return of circulation to a previously ischemic limb is followed by a certain pattern in the restoration of various Group A nerve fibres to normal activity. The most rapidly conducting afferent fibres, depressed most readily by ischemia, are the first to recover. At this time paraesthesiae make their appearance. Next in order of recovery are motor axones. Last of all, F reflexes return. Repetitive discharge, spontaneous or

evoked, has not been demonstrated on the sensory side. In the motor pathway, however, repetitive firing is very evident. This has been attributed by Kugelberg (1946) to the lowered threshold of motor fibres which he had previously demonstrated to exist during the post-ischemic phase (Kugelberg, 1944), although he presented no actual proof of this. The repetition could equally well take place at myoneural junctions, regions well-known (Kuffler, 1944) to respond in such a fashion under many conditions. It can however be stated, to anticipate the results presented in a later section of this paper, that the phenomenon is one of distal regions of the motor pathway, and not related to changes in proximal segments of nerve trunks.

C. *Modification of the Post-ischemic State*

Aided by the information which has emerged above dealing with certain features of afferent and motor activity in the post-ischemic state, it is timely to return to a consideration of the clinical phenomena which occur spontaneously under such conditions. Three additional modifications have been introduced in an attempt to throw some light on the observed features. Two have been used by previous authors in making interpretations on the basis of reported sensory experiences. Those modifications have been repeated here and subjected to careful examination. The third procedure was used to extend the analysis of mechanisms involved in paraesthesiae.

a) A second sphygmomanometer cuff (designated here as cuff B) was placed around the arm or forearm below the usual cuff (cuff A). Just prior to release of cuff A, cuff B was inflated to, and maintained at, a pressure of 200 mm. Hg. This modification, first adopted by Lewis, Pickering, and Rothschild (1931), has also been used by Merrington and Nathan (1949), and Weddell and Sinclair (1947). Far-reaching deductions have been made from the subjective results of this modification, on the assumption that cuff B, when inflated around the forearm, was equally effective in maintaining complete circulatory arrest as when it was placed well above the elbow. Weddell and Sinclair (1947) alone cast very serious doubt on the validity of this assumption.

b) Merrington and Nathan (1949) modified the picture of the post-ischemic state by prior injection of nerves with procaine. Some of their experiments have also been repeated here.

c) Finally, intra-arterial injection of d-tubocurarine chloride as described by Grob, Lilienthal, and Harvey (1947) has been introduced into a release experiment on one of the authors.

1. *Double Cuffs*

A) When cuff A was placed as high as possible *around the arm* under study, the second cuff B could be applied just below it with little or no overlap. The usual surface or needle electrodes led muscle action potentials from the hypothenar group of muscles. Cuff A was inflated to 200 mm. Hg and maintained at that level for thirty minutes or until all voluntary movement had become impossible. At that point, cuff B was inflated to a similar pressure and maintained at this level. Cuff A was then rapidly released. Several minutes later, cuff B in turn was suddenly removed.

Contrary to expectation, no paraesthesiae appeared in the distal part of the limb following release of cuff A. When cuff B was removed several minutes later, the customary outburst of paraesthesiae and movement developed. They were in all respects identical with those described in a previous section. The continuously-recorded electrical record confirmed the subjective and clinical observations. Excerpts from such a record are shown in Figure 7. Record 1 shows the absence of action potentials on attempted voluntary movement just before the interchange of cuffs. Record 2, taken one minute, and record 3, taken three minutes, after the interchange of sites of occlusion, reveal absolutely no evidence of spontaneous activity. Needless to say, all intervening strips of the record were likewise "silent". The remaining four records of the figure depict the usual outburst of electrical activity in hypothenar muscles accompanying the tightness and spasm which followed release of cuff B. This experiment shows that release of 12 centimetres of proximal nerve trunk from ischemia does not lead to paraesthesiae nor spasm.

B) When cuff A was placed high around the upper arm, cuff B around the *fleshy part of the forearm*, and the same type of experiment repeated, the interchange of cuffs was followed by a slightly different sequence. On release of cuff A, there was the usual flushing and warmth in the area between the cuffs. About forty-five seconds later, a few isolated transient tingling sensations were felt in the hand. No visible movement nor hardening of the small muscles took place. Immediately

following the minimal paraesthesiae in the hand, intense stinging sensations and tightness were felt throughout the forearm, and more markedly on the extensor aspect. The hand moved involuntarily up in slow dorsiflexion at the wrist. At this stage, power was beginning to return in the long forearm muscles. No voluntary power was present in the small muscles of the hand. No detectable improvement in subjective appreciation of stimuli applied to the hand was noted. The paraesthesiae and spasm in the forearm muscle groups ran the usual time

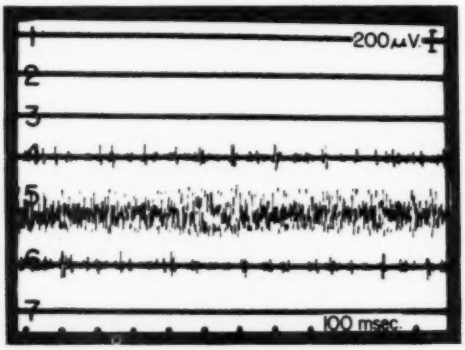

FIG. 7. Action potentials from hypothenar muscles. Continuous recording. Surface electrodes. Cuff A *high upper arm*. Cuff B *just below A*. Cuff A maintained at 200 mm. Hg for 26 minutes, then released. Record 1—attempted voluntary movement after 25 minutes of ischemia.

Cuff B inflated to 200 mm. Hg. just before release of A. Records 2 and 3 taken 1 and 3 minutes, respectively, after release of A.

Cuff B released after 4 minutes. Remaining records taken 1, 2, 4, 4½ minutes after release of B.

course which has been described above. When cuff B was released two minutes later, the customary pattern of paraesthesiae and movement developed in the hand.

The electrical records taken during this experiment are shown in Figure 8. The first record demonstrates absence of action potentials during attempted voluntary movement just before the interchange of cuffs. Record 2 is an excerpt taken one and a half minutes after the interchange—at the time when the minimal paraesthesiae in the hand were felt. There was clearly an outburst, although a meagre one, of

action potentials at that stage. It was, however, short-lived. Record 3, taken thirty seconds later, showed that it had vanished. Subjectively, the paraesthesiae had likewise disappeared at that time. The remaining excerpts in the figure portray the usual pattern found in the hand muscles following release of the lower cuff.

The occluding effects of a second cuff around the upper arm, therefore, prevented the appearance of the phenomena usually produced by the release of an adjacent, more proximal, cuff. When, however, the

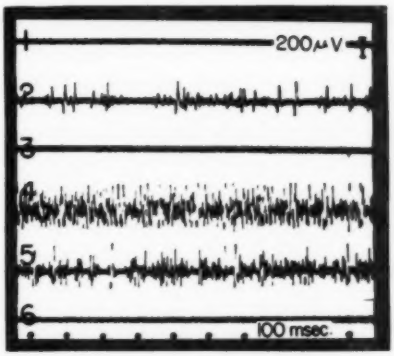

FIG. 8. Action potentials from hypothenar muscles. Continuous recording. Cuff A *high upper arm*, maintained at 200 mm. Hg for 30 minutes, then released. Record 1—attempted voluntary movement after 29 minutes of ischemia.

Cuff B, around *fleshy part of forearm*, inflated to 200 mm. Hg. just before release of A. Records 2 and 3 taken 2½ and 3 minutes, respectively, after release of A.

Cuff B released after 5 minutes. Remaining records taken 1½, 3½, 4½ minutes after release of B.

second cuff was placed further distally, in the proximal part of the forearm, the release phenomena, though greatly reduced, still appeared to some extent. Discussion of this discrepancy will be deferred to a later point in this paper.

2. *Procaine Blocks*

A) Merrington and Nathan (1949) have drawn attention to the possibility of widespread diffusion of procaine when blocks are attempted. An earlier paper (Magladery and McDougal, 1950) stressed the neces-

sity of accurate intraneural injection for complete and prolonged interruption of nerve conduction.[2] In experiments of the following type, therefore, rigid adherence to detail was maintained. The sphygmomanometer cuff was applied around the fleshy upper part of the forearm. The ulnar nerve was then injected intraneurally, in a proximal direction, above the medial epicondyle, about 8 centimetres above the upper border of the cuff. The pressure was then raised to 200 mm. Hg. Stimulation of the ulnar nerve above the block produced no action potentials in hypothenar muscles. This was found to be true at the beginning of occlusion and also five minutes after restoration of circulation. For more localized recording in this experiment, a concentric needle electrode (Adrian and Bronk, 1929) was used, rather than the

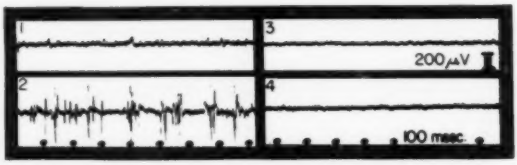

FIG. 9. Action potentials hypothenar muscles. Continuous recording. Concentric needle electrode. *Procaine block* to ulnar nerve at elbow. Pressure cuff around fleshy part of *forearm* released after 28 minutes at 200 mm. Hg. Records 1 and 2—baseline and weak voluntary movement before block. Records 3 and 4 taken 1 and 2 minutes, respectively, after release of cuff.

usual leads. Previous experience had shown that the post-ischemic spasm is readily recorded by this type of electrode.

When the cuff was released, the usual paraesthesiae and spasm ensued, *except* in the distribution of the ulnar nerve. There, no paraesthesiae were felt, and no muscle movement occurred. Figure 9 illustrates the electrical findings during such an experiment. Record 1 shows the baseline before procaine block. In record 2 are seen action potentials which accompanied weak voluntary movement before the injection. Records 3 and 4 were taken from the hypothenar muscles at thirty second intervals during the stage when the remainder of the hand and forearm manifested the most intense paraesthesiae and spasm. There was no outburst of action potentials.

[2] The authors are grateful to Dr. M. Edgerton of the Department of Surgery for his skill and continued cooperation in performing all the blocks.

In this experiment the complete procaine block was entirely central to the site of the occluding cuff. The results indicate, therefore, that the spasm of the post-ischemic state is not dependent primarily on increased excitability of motor components. It must, of necessity, be mediated through spinal cord reflexes activated through afferent pathways.

B) The corollary of the last experiment was performed by placing the sphygmomanometer cuff around the highest possible region of the upper arm. The lower border of the cuff, in the experiment to be described in illustration of all similar studies, was 6 centimetres above the most proximal antecubital crease anteriorly, and 13 centimetres above the upper part of the medial epicondyle posteromedially. The ulnar nerve was injected intraneurally in a distal direction, in the groove behind the medial epicondyle. The pressure cuff was then immediately inflated to 200 mm. Hg. The median nerve was next injected as far distally as possible in the cubital fossa. It was difficult to check the degree of local spread of procaine in the median nerve by electrical stimulation. It was found, however, that stimulation of the ulnar nerve 3 centimetres above the site of injection elicited the usual characteristic sensation produced when a shock is applied to a normal nerve by this method, but no distal motor response. Stimulation 4 centimetres below the site of injection evoked a good contraction in the appropriate muscles of the hand. These check findings were found to be the same at the time of inflation of the cuff and also forty minutes later, after release from ischemia.

Occlusion produced the customary chain of events which has been described previously, modified by the addition of the blocks. On release of the cuff, flushing and warmth appeared as usual. After forty-five seconds, stinging paraesthesiae and tightness made their appearance *in the forearm and the dorsal aspects of the proximal part of the thumb and first two fingers*, namely in the peripheral distribution of the radial nerve which had not been blocked with procaine. They increased to the usual maximal intensity and were accompanied by slow involuntary dorsiflexion at the wrist. These phenomena all subsided over the time course already described.

No paraesthesiae were felt in the palm of the hand nor volar aspects of the fingers. There was no tightening. The muscles did not become firm, and no movement was visible. Figures 10 and 11 are representative of electrical records made during such an experiment. Particular

attention is directed to the last record of each figure. Both were taken from hypothenar muscles during the period when the most intense paraesthesiae and spasm were occurring in the forearm. Clearly no action potentials were present.

When stimulation of the ulnar nerve in the forearm was performed at

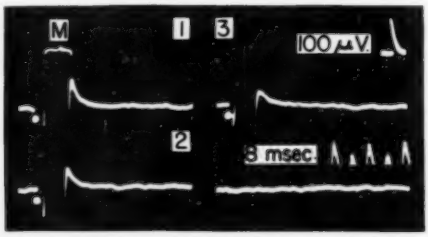

FIG. 10. Action potentials from hypothenar muscles following single maximal shocks to ulnar nerve in lower forearm. Surface electrodes. *Procaine block* to ulnar and median nerves at elbow. Pressure cuff *upper arm* released after 40 minutes of ischemia.

Records 1, 2, and 3 taken after 5, 10, and 38 minutes, respectively, of ischemia Record 4 shows inactive baseline 2 minutes after release of cuff.

FIG. 11. Continuous recording of experiment exemplified by Figure 10. Record 1 taken after 5 minutes of ischemia. Record 2 shows inactive baseline 2 minutes after release of cuff.

regular intervals following restoration of circulation, the repetitive firing of motor components in response to single shocks which was mentioned above appeared in its usual form. The successive records of Figure 12 illustrate this finding. The repetitive discharge first appeared three minutes after cuff release. The phenomenon had subsided sixteen minutes later. At no time was there any evidence of the deflections of the F reflex nor of late waves.

These results show, therefore, that an effective block of ulnar and

median nerves about 20 or 25 centimetres below the upper border of an occluding cuff prevents subjective appreciation of the sensory experiences which normally follow the release of such a cuff. They indicate that restoration of circulation to long stretches of proximal segments of previously ischemic nerve trunks does not lead to the well known paraesthesiae. On the contrary, the phenomena arise further peripherally. Likewise, the results confirm the reflex nature of the normally encountered spasm by showing that, although heightened excitability of

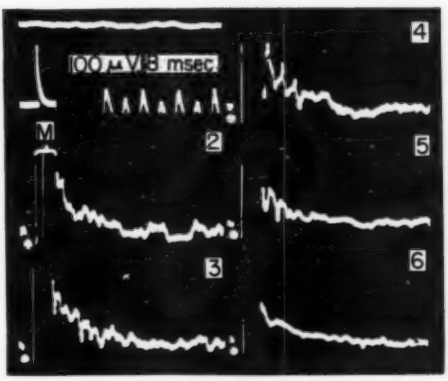

FIG. 12. Action potentials hypothenar muscles following single maximal shocks to ulnar nerve in lower forearm. Surface electrodes. *Procaine block* to ulnar and median nerves at elbow. Pressure cuff upper arm released after 40 minutes of ischemia. Record 1—inactive baseline 2 minutes after release of cuff. Remaining records taken 4, 6, 8, 9, 20 minutes, respectively, after release of ischemia.

distal motor fibres, myoneural junctions, or muscle does exist under these circumstances, it does not lead to spontaneous spasm.

3. *Intra-arterial Curare*

Curare, to date, has been used only once in studying the phenomena of the post-ischemic state. An indwelling cannula was placed in the brachial artery in the cubital fossa. The sphygmomanometer cuff on the upper arm was then inflated to 200 mm. Hg. and maintained at that level until voluntary movement in the hand was abolished—a period of thirty four minutes. Ten units of d-tubocurarine (Squibb) in 1 cc. of saline were then injected into the artery. The cuff pressure was lowered

momentarily to 100 mm. Hg. to permit distal spread of the material, and immediately restored to its previous level. Six minutes later, the cuff was released.

The injection of the d-tubocurarine was followed immediately by a transient burning sensation down the forearm and hand which is nor-

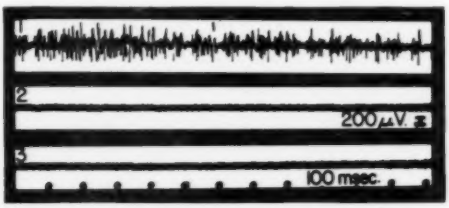

FIG. 13. Action potentials hypothenar muscles. Continuous recording. Surface electrodes. Indwelling cannula in brachial artery. Cuff upper arm released after 31 minutes at 200 mm. Hg. 10 units *d-tubocurarine* into artery 6 minutes before release. Record 1—voluntary movement before cuff. Record 2—1½ minutes after release of ischemia. Record 3—attempted voluntary movement 5 minutes after release of cuff.

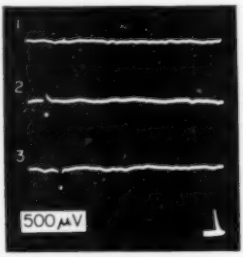

FIG. 14. (Same experiment as Figure 13—cathode ray records.)

Record 1—1½ minutes after release of cuff. Records 2 and 3—single maximal shocks to ulnar nerve at elbow 2 and 6 minutes, respectively, after release of ischemia.

mally experienced with this procedure (Grob, Lilienthal, and Harvey, 1947). No movement of the limb occurred. No other paraesthesiae followed the brief drop in cuff pressure. No action potentials appeared with continuous recording from the hypothenar muscles. The release of the cuff six minutes after injection was followed by all the usual paraes-

thesiae. The stinging sensations and tightness were considered by the subject to be comparable in every way to those following the unmodified release of ischemia. There was, however, no clinical change in the flaccid condition of the muscles, no movement occurred, and no electrical activity could be recorded.

Figure 13 contains excerpts from the electrical records of this experiment. In record 1, action potentials which accompanied voluntary movement at the beginning of the experiment are shown. Record 2 was taken during the most intense phase of the paraesthesiae. The final record shows the flat baseline when the subject attempted voluntary movement four minutes after the tightness had subsided. In Figure 14 more detailed records indicate the same result. For added check on the adequacy of curarization, maximal shocks were applied to the ulnar nerve in the forearm. As can be seen in records 2 and 3 of this figure, no action potentials could be recorded from hypothenar muscles.

Curare, therefore, though blocking initiation of the usual post-ischemic spasm in hypothenar muscles, leaves the sensory phenomena unchanged. The latter then, are not secondary to actual contraction of muscle fibres, and must be activated by some other means.

DISCUSSION

The fact that paraesthesiae follow restoration of circulation to a previously ischemic limb is well known—Reid (1931), Lewis, Pickering, and Rothschild (1931), Weddell and Sinclair (1947), Kugelberg (1946), Merrington and Nathan (1949), and others. That these can be divided up into separate groups and analyzed in detail may justifiably be questioned. Of more importance, however, is to point out that a motor component, although denied by Lewis, Pickering, and Rothschild (1931), exists under such conditions. It was clearly described by Reid (1931). The demonstration in the present paper of this motor component, and its dependence on spinal cord reflex activity, indicates that the term "pseudocramp" is a misnomer. It might perhaps, be suggested that the lengths of occlusion used in this investigation were excessive and that only "pseudocramp" occurred after shorter periods of circulatory arrest. It should, therefore, be added that ischemia of as short a duration as fifteen minutes is succeeded by a comparable motor activity. It has not seemed profitable to carry out a large number of experi-

ments to establish some crucial period, short of which the phenomenon does not occur.

There seems little question but that release of ischemia leads to a heightened excitability of some elements distal to the upper border of the occluding cuff which is manifested clinically as paraesthesiae and muscle contractions. There would seem, theoretically, to be two alternatives possible:

a) that all excitable tissues are subject to the depressant action of ischemia and, on restoration of circulation, show a heightened excitability. Some tissues, or parts of such, may be relatively more susceptible or resistant to the process than others, yet none are excluded from sharing in it;

b) that only some elements are affected, or even specific parts of some tissues, to the relative exclusion of others. The influence of Lewis, Pickering, and Rothschild (1931) has been strong in directing the attention of investigators to specific regions and structures (vide. Weddell and Sinclair, 1947, Kugelberg, 1946, and others). Merrington and Nathan (1949) had a broader conception than others, but even they strove hard to rule out certain endings, and ignored motor elements.

It has seemed to the present investigators that on general grounds the second alternative is unlikely. Certain experiments have been embodied in this study to test the validity of previous observations on which the exclusive statements have been made. It might be well, at this juncture, to consider the evidence one way or the other.

The mere presence of paraesthesiae presumably indicates repetitive discharge of some sensory elements distal to the upper limit of the preceding cuff pressure. This could theoretically occur in sensory endings or in afferent nerve fibres. It has been demonstrated in this paper that the return of circulation to 20 to 25 centimetres of proximal nerve alone does not lead to paraesthesiae. There seems no good reason to expect that more distal stretches of nerve should differ from the proximal segments in this potentiality of initiating paraesthesiae. It would seem more likely that the paraesthesiae arise from sensory endings (Weddell and Sinclair, 1947).

The actual demonstration of a depressant action of ischemia on sensory endings in man has not yet been forthcoming, although Matthews (1933) indicated that in cats certain muscle end organs early lose

excitability under such conditions. Similarly, there is no very good evidence bearing on the possibility of increased excitability during the post-ischemic state. Previous authors have used the purely subjective assessments of patients to support arguments for and against participation of sensory endings in the initiation of paraesthesiae. Certainly the report by Weddell and Sinclair (1947) that forearm amputees do not experience paraesthesiae seems just as convincing as the statement of Merrington and Nathan (1949) that two of seven amputees did have that experience. Furthermore, the validity of the results of ingenious experiments of the last named authors with celloidin—undertaken to exclude superficial sensory endings from return of blood flow—seems open to question. The possibility of errors in using patients in purely subjective assessments has already been indicated. Too much emphasis must not be placed on the results of such clinical studies. It can only be stated, therefore, that though there may easily be a heightened excitability of proximal portions of afferent fibres in the post-ischemic state, it has not been demonstrated, and it does not lead to the production of the paraesthesiae which we have described in this paper. The conflicting results of two cuff and procaine experiments described by Merrington and Nathan (1949) need explanation. Attention has already been directed to the difficulty in detecting incomplete nerve blocks. Another difficulty might conceivably arise in distinguishing intense paraesthesiae in distal forearm and dorsum of hand from those in the volar aspect.

A reasonable explanation of the slight discrepancy between the results of two cuff experiments in arm and forearm, has already been proposed by Weddell and Sinclair (1947). They suggested that the forearm cuff does not indeed maintain complete circulatory arrest. The substantiation of this proposal is clearly of importance. The authors of the present paper have, therefore, applied double cuffs to arms and forearms of patients prior to operations on the hand.[3] Whereas in subjects with blood pressures in the usual range, cuff pressures in the arm of about 140 or 150 mm. Hg. effectively prevented oozing in the wound, forearm pressures of 60 or 70 mm. Hg. higher were needed to achieve the same result. Indeed, in one normotensive case, a pressure of

[3] The authors are grateful to members of the staff of the Department of Surgery for their help and cooperation.

200 mm. Hg. in the forearm still permitted some bleeding in the operative field, although upper arm occlusion at a much lower pressure was effective. It seems clear that any interpretation of the results of cuff pressure in the forearm which assume complete arrest of circulation must be discounted.

Merrington and Nathan (1949) suggested that rapidly conducting fibres, presumably subserving touch, are involved in the paraesthesiae. Kugelberg (1944) apparently considered, from the qualities of the experiences, that small pain fibres are responsible. The results presented in this paper show that the most rapidly conducting fibres contributing to the early part of the sensory wave (Figure 6) become excitable at the moment that paraesthesiae are first felt, and are therefore presumably available to convey showers of impulses centrally. Furthermore they have indicated that paraesthesiae and spasm occur about the time that H reflexes, known to be subserved by afferent fibres of high conduction velocity, reappear prominently. In some instances paraesthesiae have developed in distal portions of the limb even before the motor fibres supplying those parts have recovered. It seems likely, therefore, that impulses associated with post-ischemic paraesthesiae are conducted centrally by the more rapidly conducting fibres of the A group.

There is also good evidence of increased excitability in certain motor components in man after release from ischemia. Kugelberg (1944) demonstrated a lowered threshold of motor nerve fibres to constant current stimulation during that phase. Later (Kugelberg, 1946), he showed repetitive responses of motor components to single shocks under the same conditions, and assumed that he was dealing with nerve axones. The influence of Lewis, Pickering, and Rothschild (1931) apparently directed his attention to the region under, or immediately distal to, the occluding cuff—a region to which he refers as a trigger zone. Reference to Figure 11, taken from an experiment in which, although a procaine block intervened between the cuff and point of stimulation, repetitive firing still took place, tends to discount such an explanation. There seems little doubt that the heightened excitability on the motor side exists distally. It could occur in distal fibres but, for reasons already given, myoneural junctions may seem the more probable site. Whether similar changes occur in muscle fibres is not known. The experiment with curare described above, suggests that spontaneous

firing in muscle does not take place. However, more crucial evidence might come from a study of thresholds to direct stimulation in a curarized limb during this phase, or an investigation into possible potentiating effects of the post-ischemic state on fibrillations of denervated muscle (Denny-Brown and Pennybacker, 1938), (Solandt and Magladery, 1940). Such evidence is not available.

The mechanism of the spasm has been clarified to some extent. It is well known that increased excitability of motor components under conditions of tetany may lead, per se, to muscle contraction (Harvey and Lilienthal, 1942), (Kuffler, 1945), (Kugelberg, 1946). Figures 2, 3, and 12 of this paper, essentially in agreement with the results of Kugelberg (1946), show that repetitive muscle discharges can be initiated by a single nerve shock during the heightened excitability following release from ischemia. This, however, is not the explanation of the spasm occurring spontaneously after restoration of circulation. The experiments utilizing procaine blocks have shown its dependence on a reflex response to activity on the afferent side.

No clear evidence on the nature of mechanisms underlying the repetitive discharge of distal sensory components (presumably endings) is forthcoming in the present paper. Pertinent, however, is the observation that paraesthesiae were unchanged in the curarized limb, although the motor component was absent. This seems to eliminate the possibility that actual deformation of muscle or tendon endings by contracting muscle is a factor in their production.

Weddell and Sinclair (1947) considered and rejected the possibility that hyperexcitability of sensory endings, which they considered the probable basis of the paraesthesiae, could be entirely due to release from anoxia. It is interesting that Lewis (1927) made a similar exclusion in the case of reactive hyperemia. Weddell and Sinclair, like Lewis in the instance just cited, postulated venous obstruction and the ensuing accumulation of metabolites in tissue spaces as the prime result of ischemia. Release from such, with subsequent removal of the metabolites, was suggested as the factor responsible for the subsequent hyperexcitability of the endings. No definitive evidence of the nature of the presumed metabolite has, however, been produced.

Although it seems likely that many normal or abnormal tissue substances might undergo tremendous changes under these conditions of

circulatory arrest, the authors know of no clear-cut information on the subject. Of some relevance, however, are the findings of Harpuder and Stein (1943). Lactic acid, histamine, adrenalin, and potassium ions were all examined as possible contributors to ischemic pain associated with exercise. Only the potassium values were consistently elevated in venous samples taken following restoration of circulation to the limb. That this elevation is not necessarily related to work performed is suggested by animal experiments of Baetjer (1935) which showed that an 80 per cent reduction of flow to an unexercised limb produced a 60 per cent increase in venous potassium from the limb. Apparently arrest of circulation to a limb and its restoration are accompanied by important shifts of potassium ions to and from interstitial tissues and blood stream. The authors know of no direct evidence that such shifts lead to repetitive discharge of sensory endings. The extreme pain evoked by intra-arterial injection of potassium salts has, however, been vividly described by Harpuder and Stein (1943). Likewise, the common finding of distal paraesthesiae in clinical entities associated with disturbances in potassium equilibrium may rest on such a basis. That increases in extra-cellular potassium lead to marked changes in excitability of motor elements has, on the other hand, been amply demonstrated. Kuffler (1945), for example, showed that application of the ion in isotonic saline to isolated nerve-muscle preparations set up impulses along the whole length of muscle fibres, including endplate-free regions. Walker (1947) found in the intact preparation that potassium administration led to increased tension and repetitive action potentials in muscle stimulated by single direct or indirect shocks. More recently, Eyzaguirre, Folk, Zierler, and Lilienthal (1948) have verified these results and shown that the same ion had a marked potentiating effect on repetitive muscle firing induced by 2, 4-D. It would, therefore, seem conceivable that a repetitive discharge of sensory elements might likewise depend on a distortion of potassium relationships. The studies reported in this paper cannot contribute to this aspect of the problem. The results are, however, all quite compatible with such an interpretation.

SUMMARY

It has been shown that there are sensory and motor components to the phenomena occurring after restoration of circulation to a previously

ischemic limb. The latter are reflexly induced by the former. The site of initiation of the paraesthesiae has not been identified, but there is good evidence that they arise distally, and most probably at sensory endings.

Depression of afferent fibres distal to occluding cuffs has previously been shown to be a general one, but more rapid in onset and more profound in the case of fibres, or those parts of fibres, of highest velocity. Restoration of circulation is followed by recovery in the same order. Paraesthesiae make their first appearance at a time when the most rapidly conducting fibres of the nerve recover. This suggests that impulses contributing to the appreciation of paraesthesiae probably traverse fibres of high conduction velocity, and implies that pain pathways are not likely involved.

Possible mechanisms of the initiation of paraesthesiae distally have been considered. It has been concluded that the results presented in this communication are compatible with an explanation that the phenomena are due to a restitution of normal equilibrium—presumably ionic—which had been disturbed by ischemia. Results of other workers have suggested that the shifts entailed might be those of potassium.

The authors take pleasure in acknowledging the many helpful criticisms and constructive suggestions of Drs. M. G. Larrabee, S. W. Kuffler, and J. L. Lilienthal, Jr., of this university. The continued interest and support of Dr. A. M. Harvey has been greatly appreciated.

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MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

HURD HALL, MONDAY, FEBRUARY 13, 1950

Dr. Wilkins: The first paper of the evening will be given by Dr. Thomas G. Ward.

ISOLATION AND TRANSMISSION OF THE VIRUS OF THE COMMON COLD IN CHICK EMBRYOS

The successful isolation and transmission of a non-bacterial agent capable of producing symptoms indistinguishable from those of a common cold in the chick embryo is reported. This virus-like agent has been designated Strain WW.

The nasal washing was collected by instilling about 10 ml of infusion broth (pH 7.0–7.2) into each nostril during the first 24 hours of the disease. The unfiltered nasal washing was treated with 250 units of penicillin and 2500 micrograms of streptomycin per ml and inoculated allantoically into 7 day old chick embryos. After reincubation for 6 days at 35°C. the embryos were chilled at 4°C. overnight and the allantoic fluid harvested. A 10^{-3} dilution of this fluid in infusion broth, with penicillin and streptomycin, was inoculated into a second batch of 7 day old embryos.

The material tested in human volunteers was fifth embryo passage undiluted allantoic fluid. It contained no demonstrable bacteria by aerobic and anaerobic culture technics.

Twenty human volunteers all white males age 21–26 years, inmates of the Maryland State Reformatory for Males, were selected on the basis of a medical history and a complete physical examination, including an electric nasopharyngoscope examination of the nasal cavity, to establish the absence of recognizable disease.

They were divided into two groups of 10 each and placed in isolation in separate wards of the hospital at the Reformatory.

After five days preliminary isolation the volunteers were inoculated by having the person lie face up with a pillow beneath his shoulders, with the head tilted back so that the floor of the nose was at an angle of about 90 degrees to the horizontal.

One group of 10 volunteers in one ward received virus inoculum and the other group received control material.

It is emphasized that the clinicians in the study were unaware of the nature of the inoculum received by each volunteer until after the clinical observations were completed and the physicians had recorded which volunteers had a cold and which did not.

After inoculation with 0.5 ml of material into each nostril on two separate occasions 6 hours apart the volunteers were observed twice daily for the signs and symptoms of a common cold.

The results are shown in the tables below:

TABLE I

Human Volunteer Experiments with Strain WW of the Common Cold

TEST	INOCULUM	RESULTS		
		Cold	No Cold	Questionable
A	Virus	6	3	0
	Control*	0	9	1
B	Virus	4	2	3
	Control**	0	10	0
C[1]	Virus	4	0	1
	Control**	0	4	0

* Control material—autoclaved virus.

** Control material—equal parts autoclaved virus and normal allantoic fluid.

[1] In Test C the nine volunteers were the group receiving control material in Test B. They were randomized and given virus or control material and remained in the same ward for an additional five days following the second inoculation. The clinicians were unaware of the nature of the inoculum received by each individual until the test was completed.

SUMMARY

The data above indicate the successful transmission of a non-bacterial agent through five passages in the chick embryo which is capable of producing a clinical syndrome not unlike the common cold in man.

Dr. Wilkins: I shall ask that we defer the discussion on this paper until after the next paper, which is to be given by Dr. Donald F. Proctor.

CLINICAL MANIFESTATIONS OF THE COMMON COLD RESULTING FROM CHICK EMBRYO INOCULUM IN HUMAN VOLUNTEERS

In 3 controlled studies carried out on 30 volunteer human subjects, signs and symptoms similar to those of the common cold developed in a significant number (61%) of those receiving chick embryo inoculum thought to contain the common cold virus. No significant differences in the status of the upper respiratory tract prior to inoculation were observed between those who received virus and contracted colds and those who received virus and failed to contract colds.

In these studies the following factors were employed in an attempt to arrive at a correct diagnosis of the common cold:

1. Subjects received full examination before the start of the experiment and, if normal, were isolated for 5 days.

2. No one in contact with the subjects knew which received control material until the completion of each study.

3. Observations of 2 physicians were recorded separately.

4. Full nose and throat examination, including electric nasopharyngoscopic examination, was repeated in the first study 72 and 96 hours after inoculation, in the second study 48, 72 and 96 hours after inoculation, and in the third study 96 hours after inoculation.

In addition to the 14 subjects who developed the common cold there were 4 subjects who also received material containing virus who were listed as doubtful. No subjects receiving the control material developed the signs and symptoms of a common cold.

Dr. Wilkins: Is Dr. Langmuir here? Would you care to open this discussion, Dr. Langmuir?

Dr. Langmuir: I hadn't anticipated being called on, but I would like to say I am very much impressed with this work, as I at least had contact with Dr. Ward and Dr. Proctor during the planning. It seems to me most appropriate to have this work carried on here at Hopkins which for the last thirty years has done a great deal of leadership in the field, with Dr. Bloomfield working on the streptococcal infection in nurses, which project was carried on at the time the streptococus was recognized; and in the period of 1928 through 1932 in joint studies the School of Hygiene, the Medical School and the Hospital went into very extensive detail on the etiology of the common cold. Dr. Perrin Long and others worked in this particular field and were successful in transmitting the common cold to chimpanzees. However, apart from these, no extensive leads were developed towards understanding the problem.

Although many others have worked at it, and demonstrated that there is a filtrable agent that will produce the common cold—and this has been done repeatedly for the last thirty years—I am not aware of anyone's being able to keep the virus for a matter of more than a few years. One of the regretable things is that the virus repeatedly has been lost and then the work cannot be carried on.

In this work it would seem quite apparent that Dr. Ward has achieved a successful passage over a series of five transfers and then has produced something in the volunteers.

There is one question I would like to ask Dr. Ward. I didn't quite catch the dilutions of the progressive inoculations and I want to raise one other question that comes to my mind. I would like to know what is the possibility of carrying the virus over from the original—not to grow the virus in the egg but merely to retain enough and really produce the same thing as before with the original material.

Dr. Long: I am very much interested in Dr. Ward's report because the history of attempts in trying to cultivate the cold virus has been a rather difficult one. The first report of successful cultivation was that made by Dr. Dochez in minced chick embryos suspended in a special type of broth. In his report, he stated that

he had been able, after serial transfer of this material through several culture generations, to reproduce cold in chimpanzees. Dr. Bliss and I tried, and a number of other people tried, to repeat that work without any success and, to the best of my knowledge, that work was never repeated outside of Dr. Dochez' laboratory.

Then we must remember the work of Dr. Atlas in which, a year or two ago, he apparently had a virus of the common cold in eggs. This was raised through a number of generations and then was lost. I have read that Dr. Andrewes thinks he has had the same experience. It is an extremely difficult problem.

And then another thing that makes all this work difficult, Dr. Frost—after the epidemiological work done under the auspices of the Abel fund between 1928 and 1932—felt that it looked as though we were probably dealing with a number of viruses which produced the symptom complex that we call the common cold. I know he was of the opinion—because I talked about it with him many times—that the question of producing immunity by taking a large amount of virus and treating it so as to inactivate it, but not to alter its antigenic status, might or might not work as an immunizing agent because one might be encountering scores of different viruses in epidemics or endemics of colds.

I would like to ask Dr. Ward if he was able to pick up similar agents from other people with the common cold? I would also like to know whether the virus is easy to pick up from every individual who has a common cold.

Dr. Fisher: I would like to ask Dr. Ward and Dr. Proctor whether or not they were able to take filtrations from these volunteers and pass it on that way. I would also like to ask whether or not the evidence that the virus was growing in the chick embryo was studied by a histological method. Is there any way you could recognize it?

Dr. Wilkins: Are there any further questions? Dr. Ward.

Dr. Ward: In reply to Dr. Langmuir's question I would like to re-emphasize and clarify the passage of this material, because I believe we are a long way from the original nasal washing. I didn't go into that in too much detail as there really wasn't time. A chick embryo at seven days has about 2 or 3 ml of allantoic fluid. If it is inoculated with approximately 1/10 ml of allantoic fluid and allowed to grow for about six days, there will be approximately 10 ml of allantoic fluid. Therefore, the original material in that first embryo is diluted 10^{-2}. One-tenth ml in 10 is 10^{-2}. We took that 10^{-2} material and diluted it to 10^{-3}, and inoculated this dilution into a second chick embryo. This gives a dilution of 10^{-5} of the original material. If this be carried through five passages in the chick embryo, as we did, the dilution of the original inoculum approaches 10^{-22}. As to whether we carried along a small bit of mucous material from embryo to embryo I don't know. It seems unlikely.

With regard to Dr. Long's questions, we have only tested this strain in human volunteers. I, for one, in our present state of knowledge, would not accept a definition of a common cold virus other than one which is capable of producing disease in man. We do have a technique which we think is fair and apparently, in seven

nasal washings that have been tested, three gave us a so-called positive specific radioactive ratio. I am afraid time does not permit a discussion on this point as it is rather complicated and the data is not too definitive just now.

I would answer your question "Can we pick it up at any time?" with an emphatic *NO*. I would be surprised if we are successful in isolating strains from more than 25% of cases. With Influenza B virus, we are successful in about 40% of the trials. I would be hesitant to reason by analogy from Influenza B to the common cold, but it is the nearest thing in the virus field we know anything about at the moment. If the common cold virus could have been isolated easily in chick embryos I am surprised it hasn't been done long ago.

We have not tested nasal washings of the volunteers by checking them back in volunteers, Dr. Fisher. We were able to carry out these three tests and then we ran out of money. The important question to answer at this time, and the only one we were trying to establish, is that this material, which has been passaged five times, in chick embryos is able to produce a clinical syndrome not unlike the common cold in man.

There is no evidence grossly, or by looking at the fluid, that the chick embryo is affected with Strain WW of the common cold virus. We have not done histologic studies.

Dr. Wilkins: As Dr. Langmuir pointed out, Hopkins has played a very prominent place in the study of the common cold. I think the next two papers are another field in which Hopkins has been of very great importance. I remember up until a few years ago we were frequently faced with the deaf baby and were unable to decide whether he was deaf or not, or whether he was mentally defective, and our best otolaryngologists were unable to give us the answer. Only within the past few years has work been done in the clinical set-up giving us very important answers and, as I recollect, this is entirely original and pioneer work. I am not aware that other clinics have so far been started elsewhere.

The next paper will be presented in the first part by Dr. John E. Bordley and in the second part by Dr. William G. Hardy.

THE DETERMINATION AND SIGNIFICANCE OF HEARING IMPAIRMENT IN YOUNG CHILDREN

Two types of individuals suffering from hearing impairment have offered a major problem to the otologists. For years it has been recognized that those individuals suffering from psychological type hearing loss and children under the age of 6 whose hearing loss has been presumed or whose development was such as to raise the question of mental maldevelopment, have presented the difficulty of accurate hearing evaluation. It is impossible to determine the thresholds of hearing in these individuals because they are unable to accurately indicate by the usual methods of audiometry at what levels the threshold of their hearing may lie. The reason for this has been that modern audiometry is based on the voluntary response of the patient tested which is in substance a subjective response.

In order to develop a more objective method of determining hearing thresholds, the technique of psychogalvanic skin resistance response has been undertaken. This is based on a conditioned reflex which is established by studying changes in skin resistance following an auditory stimulus. It has been found that by using a standard audiometer which introduces a pure-tone into the ear and following this by a slight electrical shock, a reflex can be established whereby skin resistance changes can be recorded which take place following the stimulus and before the shock is introduced. This skin resistance change has been determined by using the skin resistance study method developed by Dr. Curt Richter and its application was suggested to us by Dr. John Whitehorn. In some 400 cases studied in children and adults, it has been established that this is an accurate method of testing and corresponds in normal individuals exactly with the standard subjective method of audiometry. By this method, approximately 200 children from 5 years to 6 months of age have been studied. In this group, the etiological factor has been determined in all but 61. The etiology ranges from virus infections of the mother during pregnancy to children's diseases in early life. About 10% of the total is accounted for by rubella in pregnancy and RH negative blood determinations in the mother. Intracranial changes account for many of these children's hearing impairment. The remainder are distributed through children's diseases in early life.

Normal development and behavior of the young children, both in terms of the use of language and of social maturity, is keyed closely to the patterns of the mind that involve auditory stimuli. An auditory impairment that interferes seriously with the processes of language-development is bound to interfere seriously with many other factors of development.

Closely related to this is the fact that the child between the ages of 2 and 6 years is at his peak as a language-learning machine, and will never again be quite so ready nor able to form the communication patterns of symbol-recognition and symbol-interpretation that constitute ordinary language. It is important, therefore, that the accurate diagnosis of auditory acuity be undertaken as early as possible.

Nowadays, when we know that the young child has a handicapping hearing impairment, we want to start to work with him as early as age 2 in the special communicative skills that he needs to learn in order to compensate for the hearing impairment. This involves training with amplification, work with speech (lip) reading and speech training—all combined with auditory training as a composite attack on the problem of communicative disability. (Demonstration of acoustic distortion by phonographic records.) Two facts are of primary importance: (1) few young children, whether they are considered congenitally or adventitiously impaired, are totally without residual hearing; (2) modern electric amplification, employed carefully as part of a whole developmental regimen, can readily reach children who ten years ago were considered irredeemably deaf. It is true that the child with a profound hearing loss, but otherwise normal, will need special

education but he is not to be dismissed in those terms and parents told to wait until he is old enough to go to school. Development does not wait, whether it be appropriate or inappropriate development, and special handling should begin as early as possible.

Some of the problems of differential diagnosis, important so far as objective audiometry is concerned, involve cases in which mental imparity is questioned, or in which autism or aphasia is possible. In all such problems, the determination of auditory acuity seems indicated as an early diagnostic step. It is worth noting that many cases previously classified as congenital are being analyzed nowadays in terms of specific etiology. This is a rich field for analysis and preventive measures.

Dr. Wilkins: These papers are open for discussion and questions. Dr. Stacy Guild, have you something to add here?

Dr. Guild: The work reported this evening has been of much interest to me, as it must be to all who, like myself, have for years tried to determine the hearing acuity of very young children by their responses to the subjective tests.

Two items that the speakers omitted from their presentation of the topic might be mentioned briefly at this time. The first, of which those of you not connected with the field may not be aware, is that all normal children learn to speak by imitation of what they hear. The learning by imitation extends even to the local dialect of the language. The relationship between ability to hear and learning to speak is thus very close indeed. The second item concerns myelinization of tracts in the central nervous system. From that morphological viewpoint, it is at least theoretically important that a deaf child receive training on how to speak during the period when the pathways concerned with voice production and control are undergoing myelinization, which is long before the age at which special schools for the deaf usually will accept children as pupils.

Both Dr. Bordley and Dr. Hardy are, I am sure, well aware of the items mentioned, and their omission of them was probably due solely to the lack of sufficient time to present all the reasons why an early determination should be made of the true hearing acuity of a child suspected of being deaf.

Dr. Wilkins: Is there further discussion or are there any questions?

I would like to add for myself, as a pediatrician, what a wonderful advance this has been. Those who have not been in contact with this problem can really not appreciate the difficulty of differentiating a mentally defective child from a deaf child. The problem has come up again and again over many years. The children cut off from this communication may become perfectly wild—different children from the normal—and can readily be mistaken for severely mentally defective children although they have normal intelligence. Furthermore, we have often seen children who are deaf, and who are the sons and daughters of doctors and intelligent people who have let them go to two, three, four years of age without even realizing that they were deaf.

Would you care to close the discussion, Dr. Bordley?

Dr. Bordley: I really have nothing more to add except to say that the problem as to a lot of the causes for this early hearing impairment of children is still unsolved. The more we study it, as Dr. Hardy said, the more we realize that we have been missing out on the etiology of early deafness because we have been unable to establish the hearing loss early enough in many cases to get a proper history, to get a proper lead as to what is the cause of the lesion. The more we study it the less we use the word congenital.

Dr. Wilkins: The meeting is adjourned.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Bulletin)

The Physiological Basis of Medical Practice. A Text in Applied Physiology, 5th edition. By CHARLES H. BEST and NORMAN B. TAYLOR. 1330 pp. $11.00. *The Williams & Wilkins Co., Baltimore, Md.*

This familiar and extraordinary textbook so obviously fills a need that it is reputed widely to be one of the outstanding publishing successes in the entire field of biological and medical sciences. It is a success fully deserved for a number of reasons. First, it accomplishes its stated purpose: "to link the laboratory and the clinic" and to show "how great has been the part which physiological discoveries have played in the progress of medicine, and that the practice of today has evolved from the 'theories' of yesterday". To do this the authors have made a felicitous selection of examples of disordered function to illustrate the normal mechanisms under discussion. Second, a mass of experimental information has been well digested and presented with simple clarity so that reading this text is as effortless as the subject matter permits. There can never be a textbook which satisfies every reader in the fields of his particular interest, for space limitations require rigid selection of material for discussion. The reader will be struck by the overall discrimination with which the selection of material has been made. Generous bibliographies provide a broad basis for the person who would pursue the special fields into finer ramifications.

This text has been written by but two authors, with a few brief sections contributed by collaborators. The consistent excellence of the many essays which compose the text make this book an impressive feat of skill and scholarship, especially when symposia are the order of the day.

This textbook can be recommended heartily to all medical students. All who are interested in biological and medical sciences will find it an engaging and pleasant way to bring up to date their basic knowledge in fields in which they may have grown rusty.

J. L. L., JR.

Malariology. 2 vols. Edited by Mark F. Boyd. 1643 pp. $35.00. *W. B. Saunders Co., Philadelphia, Pa.*

During the early campaigns in the Southwest Pacific when malaria was wreaking impartial havoc on troops of the Allied and Japanese commands, there was but one known copy of Boyd's "Introduction to Malariology" in the theater. This had been published in 1930 and had been out of print some years before the war. But

for complete and authoritative information it was the best general text extant. Some time during World War II, Dr. Boyd started what is in many ways a tremendous expansion of that original text. In the new edition he has enlisted the talents of sixty-four authorities. Yet the book bears the impress of his own work throughout.

One does not need to remind the malariologist of the complexity of his subject. The practicing physician or research worker, however, may have forgotten that knowledge of malaria and its control involve most of the scientific disciplines. The instinct driven, patterned behaviour of anophelines, the complicated problems of insect taxonomy, the mode of action of drugs upon parasites, the symptomatology of the most protean of infections, the influence of geography on disease, the statistical evaluation of man's striving to rid himself of a great scourge, are all a part of it. Such complexity makes necessary the collaboration of many specialists in an exhaustive general textbook, and also makes it difficult for one reviewer to consider some 1500 pages of specialized knowledge.

These volumes are, without doubt, the best in the field. Coverage of all fields is detailed and encyclopedic. It is a book written for anyone who studies malaria, whether he be in Africa, India, or New Guinea. Most of the world authorities have contributed a chapter on their particular subject. With all this on the credit side, two faults warrant critical appraisal. The reproductions are poor and, in general, uninspired. Old, worn-out illustrations have been continued. It is particularly unfortunate that no color plates illumine the study of the parasite itself. The second fault is that much of the information is four years old when published. The contributors have either not cared to revise their chapters since writing them or have not had the chance. This is of some importance in that a saner evaluation of paludrine, a more complete exposition of the efficacy of residual DDT spraying, and a greater knowledge of the pre-erythrocytic stages of P. vivax and P. falciparum is available today. There are minor disagreements. One author advocates treating malaria on the basis of clinical findings, while another points out the indispensability of the laboratory. One author emphasizes the importance of intravascular clumping of blood during infection; another fails to find any evidence of it. Such disagreement is, however, natural and stimulating. There are a few weak chapters and many strong ones.

Without reservation this book is the authoritative treatment of the subject. Its very existence will go a long way toward fulfilling the desires of those to whom it it dedicated. "To all those whose efforts are directed to relieving mankind of one of the worst of its scourges: Malaria."

F. B. B.

Streptomycin and Dihydrostreptomycin in Tuberculosis. Reports of research including studies sponsored by the American Trudeau Society. Edited by H. M. Riggins and H. C. Hinshaw. 554 pp. *National Tuberculosis Association.*

Soon after the early work on Streptomycin gave evidence of its pronounced

effect against the tubercle bacillus, studies were began in various laboratories and hospitals in attempts to define its potency in clinical and experimental tuberculosis. A large part of this study was organized by the National Tuberculosis Association and the more pertinent reports resulting from this cooperative study are included in this volume, thus providing a ready reference and summary of the use of these antibiotics in all forms of tuberculosis. These articles have appeared previously in various journals and extend from the early report of Schatz and Waksman in November 1944 and of Feldman and Hinshaw in December 1944 through the more recent work with Dihydro-streptomycin, and include some preliminary data on the in vitro effect of Para-aminosalicylic Acid.

Early experiments by Steenken showed the importance of the immune reaction in increasing the effects of Streptomycin in experimental tuberculous infections in animals. He, as well as Youmans, reported on the common occurrence of Streptomycin-resistant organisms in their bacteriological studies; a finding that was later found to play such an important role as a limiting factor in the practical application of these antibiotics. It was soon shown in clinical trials that the most serious toxic effect of Streptomycin consisted of damage to the vestibular apparatus, a reaction chiefly related to size of dosage and duration of therapy. The emergence of highly resistant strains was found to be directly proportional to the duration of treatment, and this finding in vitro was paralleled by clinical infections that likewise proved to be resistant to Streptomycin. Fowler and Feind have made an important contribution in their careful report on the drug's toxic effects on the vestibular apparatus. They emphasize the importance of using a standardized test for vestibular dysfunction and describe methods by which patients with this type of damage can be rehabilitated.

The data on Dihydro-streptomycin indicate that it is less toxic but that it does not differ significantly from Streptomycin otherwise and that it shows approximately the same distribution in the body fluids. This book includes most of the important publications on the subject through the first half of 1949, and it can be recommended highly as a summary of current studies and methods of therapy in the field of tuberculosis.

A. M. F.

Atlas of Human Sex Anatomy, 2nd edition. By ROBERT LATOU DICKINSON. 145 pp. $10.00. *The Williams & Wilkins Co., Baltimore, Md.*

This volume presents a compilation of data, authenticated by measurements and sketches of actual observations on patients, accompanied by interpretations by the author on the basis of statements by these patients concerning intimate sex behavior. Dr. Dickinson has tried to correlate anatomical findings with physiology and behavior. He has, during fifty years of practice of gynecology and research, accumulated a tremendous amount of material. A keen observer, artist as well as scientist, a physician of unusual insight and understanding, he has made a practice of sketching and making voluminous notes on records of thousands of

his patients and it is from this remendous storehouse that the Atlas is composed. He has, moreover, in many years of intensive study of world literature, as well as interviews with scientific authorities throughout the world, critically compared their findings with his.

The author is an amazing man, a human dynamo, with a mind bursting with curiosity and new ideas for research. His special interests for many years have been problems related to fertility, sterility and sex behavior, and he is the author of numerous articles and books on these subjects. A pioneer and crusader, he has tried unceasingly to interest physicians and particularly gynecologists and obstetricians in the importance and necessity of sex education, premarital examinations and marriage counseling. Now, at 80 years of age, he is still working in his laboratory and writing.

He states that it is with the idea of furnishing accurate factual information for those physicians who do marriage counseling and as an aid to a better understanding of some of the reasons for physical maladjustment that the Atlas was published.

There is a wealth of material in this volume to be found, I believe, in no other publication, and most physicians will be surprised to find many observations previously unknown to them.

One might be critical of the text, which comprises about one-third of the Atlas, and one might differ with the author in some of his interpretations. It is true, the book could be more clearly written and better organized with some material omitted, but that is an unimportant consideration in a work which is an outstanding contribution in a field where there are great gaps in exact knowledge and where scientific information has been so unquestionably inadequate. The author admits that this volume is just a beginning and makes a plea for more extensive scientific investigation along the same lines.

The Atlas can be read with profit by most physicians, but particularly by those who are concerned with sex education, premarital and marriage counseling as a means of preventing martial discord and divorce, much of which is admittedly caused by ignorance and physical maladjustment.

B. L. M.

Mental Hygiene in Public Health. By PAUL V. LEMKAU. 396 pp. $4.50. *McGraw-Hill Book Co., New York.*

This, the first book devoted to the role of psychiatric perspectives in public health work, is primarily a textbook for the instruction of public health officers and nurses. The problem of the prophylaxis of mental illness is viewed from the broad perspective of fostering sound personality development. The public health worker, alert and informed, will find many opportunities in his work to aid individuals and groups in achieving more harmonious development and to rectify deviations while still incipient. The author traces the development of personality from birth through senescence, discussing and illustrating problems that commonly

arise at various phases of life. The picture and discussion of the social development of the person is unusually sound and well written, and should find wide circulation even outside the field of public health. The material is just as useful and necessary to physicians and nurses in other fields. It can serve very well as a text in those first year courses in psychiatry in which normal personality development is stressed. Dr. Lemkau has managed to eliminate virtually all terminology peculiar to psychiatry as a specialty and to offer a cogent view of personality development free from the dogma or prejudices of any particular school of thought without neglecting the significant contributions of any.

The reviewer cannot expect the author to write the book on mental hygiene and public health that he would like to have available. However, it is necessary to indicate that although the book presents an orientation for the integration of psychiatry and public health and reviews briefly public health measures concerning mental health undertaken in the various states, it does not seek to present a program or a definite philosophy for the development of public health work in mental hygiene. It specifically renounces discussion of the impact of broad social issues and stress such as poverty, housing, industrial relations, racial discrimination, etc., upon mental health as not being within the field of operation of the public health officer. The author refrains from promulgating or discussing programs for the improvement of mental health in communities or states. The book is a fine implement for teaching the basic data necessary to formulate such projects, and serves the practical function of educating the public officer for what he can do here and now.

T. L.

Handbook of Digestive Diseases, 2nd edition. By JOHN L. KANTOR and ANTHONY M. KASICH. 658 pp. $11.00. *The C. V. Mosby Co., St. Louis, Missouri.*

Dr. John Kantor was a dynamic person, who infused into his associates his enthusiasm for medicine. He would have reason to be pleased with Dr. Kasich's revision of his *Synopsis of Digestive Diseases*. In this small *Handbook*, information concerning the various gastrointestinal syndromes is summarized in pleasant, readable form. Moreover, the illustrations are much clearer than those in most contemporary texts of gastroenterology. The space devoted to each subject is necessarily brief. None the less, specific information is provided concerning diagnostic and therapeutic procedures. The text is usually free of the didacticism found in most synopses. As a result, this book should prove useful to the non-gastro-enterologist who wants to acquaint himself with current knowledge in this specialty.

O. D. R.

Regional Ileitis. By BURRILL B. CROHN. 229 pp. $5.50. *Grune and Stratton, New York.*

This book is more inclusive than is indicated by its title. It takes up not only

ileitis, but jejunitis, ileo-jejunitis and also ileo-colitis. It is the first monograph in English (as far as I know, in any language) on nonspecific or indeterminate small intestinal inflammatory states which are nearly always granulomatous especially in their subacute and chronic forms.

It is fitting to have it written by Crohn, one of the leaders of American gastroenterology who has contributed as well as stimulated more toward the elucidation of and has probably had greater experience with these problems than any single living individual.

This work traces the separation of terminal ileitis by Crohn, Ginzberg and Oppenheimer (1932) from the then ill-defined mass of intestinal granulomata. They gave this type of affection form and substance, as it were, by working out essentials in pathology, clinical symptoms and signs along with definite sequelae and complications as well as the offering of a therapeutic approach—surgery—in this lesion involving the last foot of the ileum. The condition has become known as "Crohn's Disease".

Their original contribution aroused so much interest that soon others described a similar lesion involving both the ileum and the jejunum, then the jejunum alone and finally Ralph Colp described a combined granulomatous form affecting both the distal ileum and cecum. All of this was done between 1932 and 1934. Since then the voluminous literature—reference is made to most of it in this book—has not altered the essentials involving pathology, diagnosis and clinical characteristics. The cumulative literature from that time deals, when it does not concern itself with a reaffirmation of what was learned between 1932 and 1935, with differences as to indications for medical and surgical management, the frequency of recurrences particularly after surgery and eventual outcome. There has been no further clarification of etiology. Crohn goes into these matters in detail, critically analyzes the literature, records his own experiences and unabashedly expresses his opinions.

The book is so divided that granulomatous processes involving the several segments of the small intestine and proximal colon, particularly the small intestine, are taken up in separate chapters as referred to in the first paragraph of this review and differences are pointed out. There is an excellent chapter on radiology.

This reviewer believes it could be well argued that in the interest of clinical clarity and simplicity, all small intestinal granulomata might best be considered as one instead of making such segmental distinctions since the differences in the clinical pictures are essentially due to the differences of location, and the sequelae, complications as well as the principles in management are similar, when not identical, for all of them.

This book fills a definite need. It is concise, well written and adequately illustrated. The publishers have done their job well too. It is unreservedly recommended. "Regional Ileitis" is an essential working tool to those internists, radiologists and surgeons who deal with these problems.

M. P.

Clinical Roentgenology of the Digestive Tract, 3rd edition. By MAURICE FELDMAN. 901 pp. $8.00. *The Williams & Wilkins Co., Baltimore, Maryland.*

In the third edition of *Clinical Roentgenology of the Digestive Tract*, Dr. Feldman again presents brief and sometimes rather superficial discussions of the common as well as most of the rare pathological conditions involving the digestive tract, with emphasis upon their radiological aspects. The format follows closely that of the second edition (1945), although there has been some revision of preexisting material and the addition of a few new subjects. There is considerable variation in the quality of the numerous radiographic reproductions.

In general the book will be of interest to the radiologist and those specializing in diseases of the digestive tract, but the amount of space devoted to relatively rare pathological conditions makes it undesirable for students and the general practitioner. It is useful as a reference text. The print size and paper are good.

R. D. S.

Atlas of Roentgenographic Positions. 2 volumes. By VINITA MERRILL. 708 pp. $30.00. *The C. V. Mosby Co., St. Louis, Missouri.*

The Atlas of Roentgenographic Positions is a carefully written, beautifully illustrated 2-volume work covering the greater part of general radiography and most of the special procedures thereof. It is well organized and presents its information to the reader in a forthright and logical manner.

From the technician's point of view, its subject matter is sufficiently broad and for those with a deeper interest, an adequate bibliography suggesting further study is provided.

Since it is an atlas, one is a bit surprised to find that such procedures as laminography, photofluorography and ocular foreign body localization have been omitted.

Both books are nicely bound, the paper is of excellent quality and the numerous illustrations are well chosen and reproduced.

J. F. R.

Resuscitation and Anesthesia for Wounded Men. By HENRY K. BEECHER. 161 pp. $5.50. *Charles C. Thomas, Springfield, Illinois.*

This book is a manual on resuscitation and anesthesia for the wounded under wartime conditions. It is based on the author's experiences as consultant in Resuscitation and Anesthesia in the Mediterranean Theater of Operations. Dr. Beecher, who is Professor of Research in Anesthesia at Harvard Medical School and Chief of the Department of Anesthesia at the Massachusetts General Hospital, states in the preface that the "book has been prepared with scissors and a pot of glue. Hardly at all with a pen." It is easy to believe this. The book is largely a compilation of previously published articles by the author and his associates and the abundant material is presented in outline form, lacking continuity and readable fluidity. There are four sections: "The Wounded Man", "Physiological Derangements in the Wounded", "Treatment of Wounded Men", and "Anesthesia for the

Wounded". Each section is made up of multiple subdivisions which make for a series of starts and stops in the reader's progress. However, concise and lucid summaries at the end of each section aid considerably in correlating the material presented. The book contains a large amount of practical information based on the author's wide experience in this field. There are many good photographs, numerous statistical tables, and an adequate index. The book will probably be of greatest value as a military manual for the anesthetist of World War III.

H. W. S., Jr.

Infection and Sepsis in Industrial Wounds of the Hand. By R. E. O. WILLIAMS and A. A. MILES, 87 pp. 1s. 6d. net. *His Majesty's Stationery Office, London, England.*

This little booklet is a valuable report of the number and types of bacteria recovered from industrial wounds of various kinds. As such it gives us a clear idea of the prevalence and types of bacteria found on the skin and in the nasopharynx. The overwhelming predominance of these same organisms in both clinically apparent and "silent" infections of wounds attests to the individual himself as the source of his infection. Quantitative data is given indicating the slight value of antiseptics applied at the time of the wound, the importance of clean handling immediately after the occurrence.

The relationship between the staphylococci found in the nasopharynx and those in the wound is further documented by typing with bacteriophage. A rational scheme of wound prophylaxis is presented.

F. B. B.

Advances in Pediatrics, vol. 4. Edited by S. Z. Levine and others. 316 pp. $6.50. *Interscience Publishers, New York.*

Volume 4 is a welcome and worthy addition to the series entitled *Advances in Pediatrics*. This volume contains seven articles, each presented by an authority in his particular field. Each article, really a short monograph, presents new facts and gives a thorough review of the literature in the field. Four of the seven articles are so timely and are on subjects of such importance, that they should appeal to the general practitioner as well as to the pediatric specialist.

Professor Lichtenstein's scholarly and common sense filled discussion of "Diet in Diabetes in Childhood" cannot but be profitable reading. Dr. Platou, in his paper on the "Treatment of Congenital Syphilis with Penicillin", speaks with the authority of wide personal experience in a field where there has been considerable controversy.

Dr. Lapin brings order to the considerable body of published information about combined immunizations in children. His paper entitled "Combined Immunization" gives an extensive review of this important subject and ends with sound practical suggestions for the most effective immunization of children against diphtheria, tetanus, and pertussis. Drs. Ingraham and Matson present a splendid paper

on "Subdural Hematoma in Infancy"; these authors point out the not infrequent occurrence of this condition, the difficulty in diagnosing it unless one is on the alert for it, and the good prognosis with proper therapy and, by inference, the poor outlook in the absence of proper therapy.

Two of the remaining papers present important but somewhat unusual syndromes appearing in children. Dr. Stur Siwe discusses at length "The Reticulo-Endothelioses in Children" and Dr. Fruendenberg "Cystinosis in Children". The remaining article is a discussion by Drs. Ruth Gross and Rustin McIntosh of Erythema Nodosum and its significance.

J. B. H.

Congenital Anomalies of the Heart and Great Vessels. By THOMAS J. DRY, ET AL. 68 pp. $4.50. *Charles C. Thomas, Springfield, Illinois.*

In 1947 the authors presented an exhibit on cardiac anomalies at the centennial meeting of the American Medical Association. According to the preface this book represents the 1947 exhibit with the addition of portraits of the pioneer investigators in the field of congenital heart disease. As an exhibit this material was, doubtless, very good but as a book it is inordinately sketchy and on the whole inadequate. Sixteen types of malformation are dealt with in summary fashion. Color plates of models, a terse descriptive paragraph or two, a photograph of an autopsy specimen, a schematic diagram, and a thoracic roentgenogram serve to dispose of each type of malformation. Excepting the models which are quite good, there is little evidence of scholarship in this presentation. One finds little basis for recommending this book to students or physicians.

H. W. S., Jr.

Erratum: In our review of *Histopathology of the Skin* by Walter F. Lever. M.D., *J. B. Lippincott Co., Philadelphia, Pa.*, Vol. 86, No: 2, February, 1950, page 121, the price of the book was erroneously listed as $20.00. The correct price is $10.00.

The Editor

BOOKS RECEIVED FOR REVIEW

Biological Actions of Sex Hormones, 2nd edition. By HAROLD BURROWS. 615 pp. $8.50. *Cambridge University Press, New York.*

Brucellosis, 2nd edition. By HAROLD J. HARRIS. 617 pp. $10.00. *Paul B. Hoeber, New York.*

The Common Diseases of the Skin, 4th edition. By R. CRANSTON LOW and G. A. GRANT PETERKIN. 282 pp. 21/-net. *Oliver & Boyd, Edinburgh, Scotland.*

Diseases of the Foot, 2nd edition. By EMIL D. W. HAUSER. 415 pp. $7.00. *W. B. Saunders Co., Philadelphia, Pa.*

Infection and Sepsis in Industrial Wounds of the Hand. By R. E. O. WILLIAMS and A. A. MILES. 87 pp. 1s. 6d. net. *His Majesty's Stationery Office, London, England.*

Microphthalmos and Anophthalmos With or Without Coincident Oligophrenia. By TORSTEN SJORGREN and TAGE LARSSON. 103 pp. *Ejnar Munksgaard, Copenhagen, Sweden.*

Mitchell-Nelson's Textbook of Pediatrics, 5th edition. Edited by WALDO E. NELSON. 1658 pp. $12.50. *W. B. Saunders Co., Philadelphia, Pa.*

The Physiological Basis of Medical Practice. A Text in Applied Physiology, 5th edition. By CHARLES H. BEST and NORMAN B. TAYLOR. 1330 pp. $11.00. *The Williams & Wilkins Co., Baltimore, Md.*

Practical Neurological Diagnosis, 4th edition. By R. GLEN SPURLING. 268 pp. $5.00. *Charles C. Thomas, Springfield, Illinois.*

Quinidine in Disorders of the Heart. By HARRY GOLD. 115 pp. $2.00. *Paul B. Hoeber, New York.*

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